WHITE PAPER

A Practical and Accessible Measure of Brain Vital Signs: the NeuroCatch® Platform

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AN UNMET NEED FOR AN OBJECTIVE, PHYSIOLOGICAL MEASUREMENT OF BRAIN FUNCTION

Brain disorders directly impact one in three Canadians.[1] Yet, healthcare lacks sensitive instruments to measure healthy brain function versus dysfunction to guide treatment and monitor recovery. Current assessments for brain health and function rely heavily on subjective self-reports. Typical examples include the Glasgow Coma Scale (used to evaluate level of conscious awareness following brain injury[2,3]) and the National Institute of Health Stroke Scale (used as a screening tool for initial stroke severity). However, these indirect behavior-based tests are reported to have misdiagnosis rates as high as 43%,[4,5] and results are often confounded by interrater variability and lack of sensitivity to mild changes.[6] Along the same line, more comprehensive tests of cognitive function often rely on neuropsychological batteries of attention, perception, memory, and executive function. Unfortunately, these assessments depend on a person's ability to produce on-demand responses, which are restricted by limitations in communication and motor movement.[7–13] Many of these subjective measures, therefore, are susceptible to extraneous influences and have inherent flaws.

An important gap in healthcare currently exists: an unmet medical need for a rapid, objective, physiological measurement of brain function in clinical settings. In essence, a *vital sign* for brain function. Potential brain vital sign measures do exist and are used primarily in research settings.[4,14] Event-related potentials (**ERPs**), measured by means of electro-encephalography (**EEG**), are well characterized in research literature[15] as a physiological measure of brain function, but the transfer of this technology to clinical settings and the frontlines of healthcare have been limited to date.

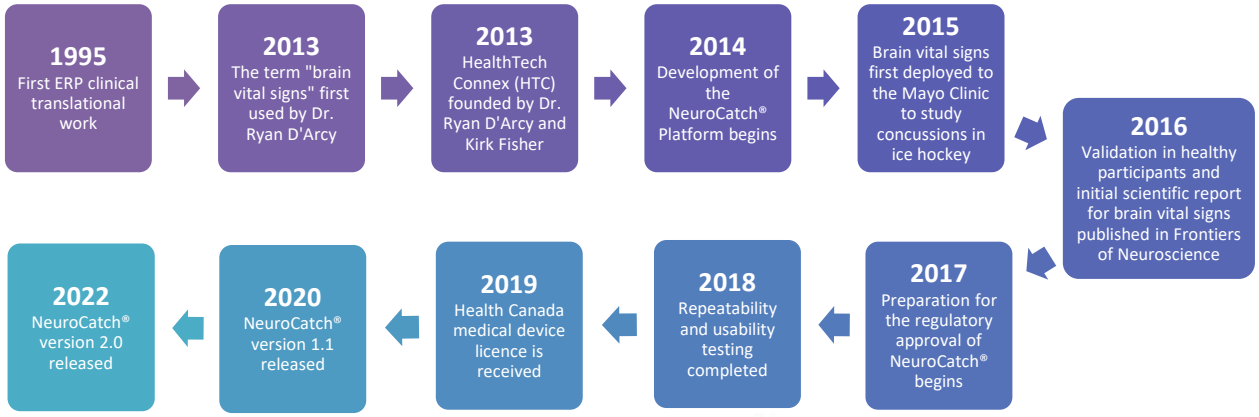

Figure 1: Brain vital sign development progress

Research & Development (R&D) into the clinical applications of ERPs dates back more than 25 years. This work has been supported by all major prestigious competitive funding agencies in Canada (Canadian Institutes of Health Research, Canada Foundation for Innovation, Mitacs, Natural Sciences and Engineering Research Council, the National Research Council etc.) and has included training of more than 250 highly qualified research personnel (e.g., PhD, MD, and Masters, Post-doctoral, and early career researchers). The team has been led by Dr. Ryan C. N. D'Arcy, PhD, PlEng who holds a BC Leadership Chair in Medical Technologies and is full tenured Professor in Clinical Neuroscience, Neuroimaging, and Neurotechnology at Simon Fraser University, University of British Columbia, and Surrey Memorial Hospital.

EVENT-RELATED POTENTIALS (ERPs)

ERPs are very small voltages generated in the brain as a response to specific stimulus events, such as listening to an auditory tone or spoken word.[16] These signals can be recorded with EEG technology using non-invasive scalp electrodes. Since the 1930s, ERPs have been extensively studied as indicators of brain function, from low-level sensory to higher-level cognitive processing.[15] In 2022, a PubMed search of "event related potentials" returned over 150,000 peer-reviewed publications dating back to 1946, with the first reported evoked response dating back to 1934[17] and over 4000 new published studies in the last year alone, representing a robust scientific foundation on which to commercialize this technology. For more than 25 years, our group has led the development of clinical

ERP applications.[7–12,18–21] This work has focused on developing rapid, automated approaches to record ERPs at an individual level.

Why ERPs now? While familiar to many, the untapped potential and economical advantage of EEG has historically been restricted to specialized laboratory settings.[14] Experimental studies were also far too lengthy (i.e., hours), complex (i.e., advanced and lengthy electrophysiological analyses), and intensive (expert dependent) to be clinically accessible. Recent engineering advances have brought the mainstream availability of portable EEG systems to the forefront, catalyzing their increased awareness and use. At the same time, historical challenges around the complexity and variability of EEG data have been recently overcome by signal processing and classification advances.[22,23] As a direct result, R&D over the past decade has enabled the development of a vital sign framework to manage brain health in a manner analogous to the clinical application of vital signs for managing heart health.

MEASURING BRAIN VITAL SIGNS

Routinely checking objective physiological vital signs, such as heart rate and blood pressure, is an essential part of preventative healthcare and key to monitoring the health of various body systems (e.g., by establishing baselines and managing risk factors). However, no such vital signs yet exist for the brain – arguably the most important organ of all.

Using blood pressure as a model, it has been possible to "reverse engineer" a vital sign framework using well-established ERPs. The brain vital sign framework compressed hours of laboratory testing to a 6-minute test that automatically elicits, analyzes, and identifies three key ERP responses along the continuum of information processing – from low-level sensation to higher-cognition.[24] Critical components of this framework include that the brain vital signs must be:

1) Well-validated and extensively characterized within the research literature;
2) EEG hardware platform independent;
3) Recorded reliably within healthy individuals across the lifespan;
4) Easily communicated and accessible to healthcare practitioners;
5) Set against reference value ranges of typical response characteristics.

The initial description of the brain vital signs framework achieved significant impact in the highly accessed *Frontiers of Neuroscience*: the article was the #1 highest attention scoring study from 2016-2020. Previous evidence of impact for our clinical ERP work includes editorials and invited reviews (in Clinical Neurophysiology and International Journal of

Psychophysiology), and citations in seminal sources and authoritative textbooks (e.g., *Neuropsychological Assessment*; Evoked Potentials on Answers.com; *Event-related potentials: A methods handbook; and Psychophysiology: Human Behavioural and Physiological Response*). With more than 52 international, peer reviewed scientific papers published (empirical, invited reviews and editorials), including five papers published in 2021,[25–29] the medical literature for brain vital signs has become well established.

BRAIN VITAL SIGNS AND THE NEUROCATCH® PLATFORM

The extensively published scientific studies that led to the translation of ERPs to a brain vital sign framework also create the foundation for the NeuroCatch® Platform. NeuroCatch® is designed to rapidly record and analyze ERP responses using portable EEG devices and providing automated, standardized and clinically intuitive results. As a Health-Canada-approved Class II medical device (Version 1.1 MDL 102616; Version 2.0 MDL 108282), with FDA registration (D476519), NeuroCatch® is underpinned by international patents and trademarks, together with extensive technical and educational materials supporting the clinical application of ERPs. After an initial deployment of the first generation of NeuroCatch® to more than 40 clinical and research centres across Canada and the USA, the second generation of NeuroCatch® rolled out in 2022 with advances in hardware, software, and analytics. Larger expansions are planned for 2025 and 2027, with intra-generational iterations in-between. The third generation will improve upon this model and is planned for 2023. HealthTech Connex oversees NeuroCatch Inc., with both companies being recognized through numerous international awards, distinctions, and media coverage.

BRAIN VITAL SIGN VALIDATION IN HEALTHY INDIVIDUALS

To begin developing brain vital signs, three highly validated[30] ERPs were selected: the **N100** (linked to auditory sensation), **P300** (linked to basic attention), and the **N400** (linked to cognitive processing). These ERPs were validated across large samples of healthy individuals.[18,27] To date, brain vital sign data has been collected on thousands of individuals and, owing to the rapid test time, evaluations of normative ranges, reliability and validity have been relatively fast to develop and predicably consistent with the existing literature. The N100, P300, and N400 are specifically elicited by standard auditory tone and spoken word pair stimuli designed to evoke sensory, attentional, and cognitive processing of unexpected events. The

speed (in milliseconds) and size (in microvolts) of the brain responses are measures and presented in an intuitive, standard report immediately after the scan (Figure 2). The three ERP components above can be elicited across sensory modalities,[30] across the lifespan,[24] and repeatedly within individuals to track change over time.[31] In healthy aging and day-to-day cognitive function monitoring, these brain vital signs show enhanced sensitivity to subtle changes in cognitive processing that cannot be detected by behaviour-based tests.[24,31]

The N100 occurs at approximately 100 milliseconds (ms) after a tone is played and represents the acknowledgement by the brain that information has entered auditory processing systems.[32] The P300 occurs at approximately 300ms after a tone is played and indexes an early stage of attentional processing; specifically, the discrimination of one event (e.g., a deviant sound or tone) from another (a standard tone).[33]

The N400 peaks at approximately 400ms after a word is played. This response occurs when unexpected or incongruent word pairs are detected (e.g., when hearing "Bread…Sing" rather than "Bread…Butter"), therefore indexing one of the highest-order cognitive functions: language processing.[21,34,35] As the highest-level cognitive response, advanced neuroimaging methods have successfully validated it through underlying functional neuroanatomy comparisons.[36]

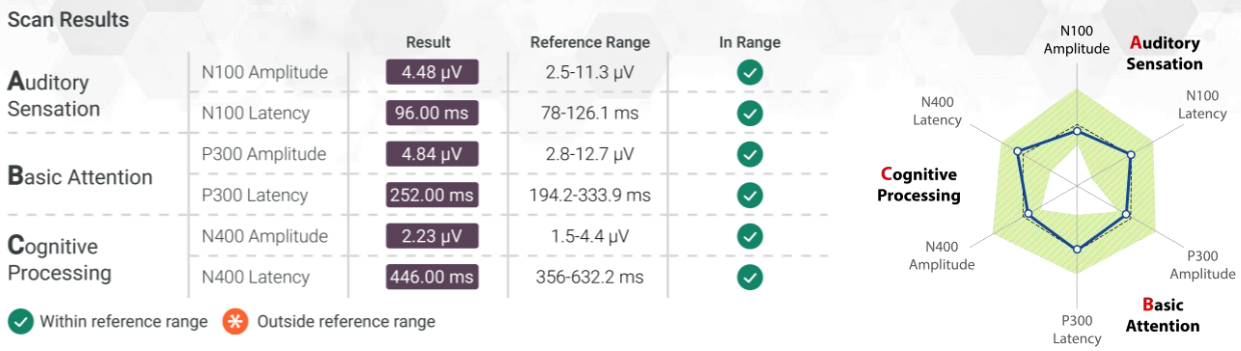

Figure 2: Sample NeuroCatch® scan results

NEUROCATCH® PLATFORM: COMMERCIAL APPLICATIONS

NeuroCatch Inc., a wholly owned subsidiary of HealthTech Connex, was established to commercialize brain vital sign science through technology development. The currently deployed NeuroCatch® Platform runs in approximately 6-minutes and is fully automated.

HealthTech Connex is a dynamic medical technology company that was co-founded by Dr. R. D'Arcy and K. Fisher and is located in the Health and Technology District, next to Surrey Memorial Hospital. The NeuroCatch® Platform is the company's flagship technology product. HealthTech Connex is an award-winning, high-tech start-up, with brain technology products and services directed towards improved access to advanced brain care. HealthTech Connex was recognized internationally by Brainnovations, the Surrey Board of Trade (SBOT) Business Excellence Award, the SBOT Innovation Award, as well as an Emerging Rocket company on BC's Ready to Rocket list.

Within British Columbia, HealthTech Connex is among the top 10% of the largest tech companies. With the NeuroCatch® Platform deployed widely across North America, HealthTech Connex has successfully expanded to include strategic global neurotechnology partnerships in both products and services.

NEUROCATCH® PLATFORM: SECOND GENERATION ADVANCES

The second generation of NeuroCatch® includes a number of advances to the sensitivity and quality of ERPs in clinical assessment.

EPiO: Through the implementation of the Evoked Potential Input/Output (EPiO)™ Adapter, the ERPs from NeuroCatch® can detect evoked responses with less than 2ms latency. This represents an approximate 10-15x improvement relative to existing off-the-shelf hardware[37]. This precision, enhanced by the EPiO™ Adapter, further enables novel analytics features that include automatic signal quality detection as well as ERP response variability.

Figure 3: Visualizing improved precision and sensitivity

Cloud: The cloud-based platform includes a client management software, allowing users to seamlessly manage their relationships with new and existing individuals.

Reference Ranges: A major goal of employing ERPs in clinical practice is to obtain a measure of cognitive function that can be used to assess an individual's brain health, through comparison to prior results or reference ranges (e.g., as seen in Figure 2). The second generation of NeuroCatch® includes these comparisons. The four key clinical application themes for the NeuroCatch® Platform in various neurological conditions are summarized below.

CLINICAL USE CASE: CONCUSSION AND TRAUMATIC BRAIN INJURY

Being able to objectively track on-going changes in brain health has large implications for those with impaired brain function. In line with this, after initial validation in healthy adults[24] and in collaboration with partners at Simon Fraser University and Surrey Memorial Hospital, the brain vital signs scientific framework was first deployed to the Mayo Clinic in a multi-year academic research program examining concussions in ice hockey.

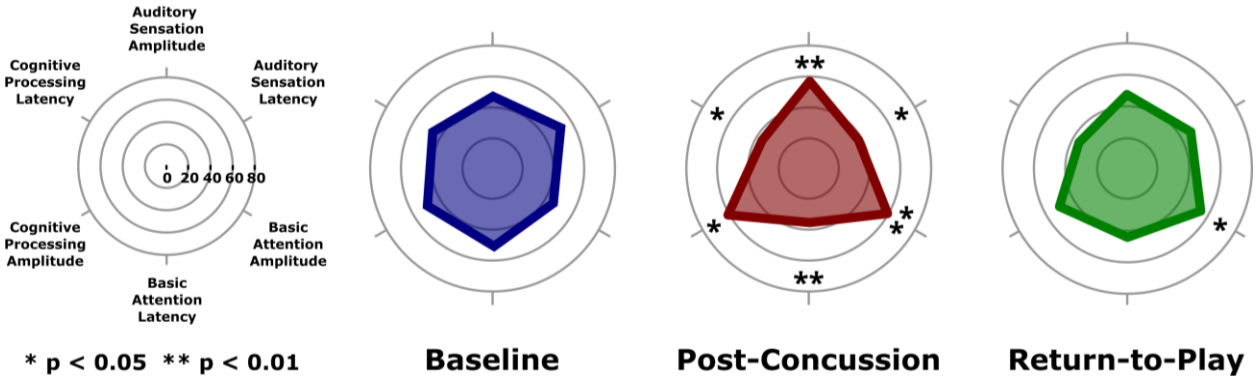

Figure 4: Mayo ice-hockey concussion results. (The research study was designed and carried out by the Mayo Clinic Sports Medicine Ice Hockey Research team, partially funded by USA Hockey and the Johannson-Gund Endowment.)

The results of this study, published in *Brain (Editor's Choice)*, showed characteristic changes in brain vital signs when hockey players were monitored between baseline, injury, and return-to-play (Figure 4). Importantly, brain vital signs changes in concussion also appeared to be associated with a specific 'profile' shape (triangular), which could help guide healthcare professionals when making clinical decisions regarding the status of recovery in concussed players (Figure 4).[38] These brain vital sign changes were consistent with previous literature showing that ERPs have enhanced sensitivity to post-concussive changes in brain function, which may not be detected by neuro-psychological tests of symptom-based reporting.[39]

A critical development in the brain vital sign framework is the translation from complex neuro-physiological waveform signals to a simplified and intuitive graphical display using a radar plot. When all 6 standardized results are plotted using radar plots, it is possible to establish a healthy brain vital signs profile: a symmetric hexagon around the 50th percentile range. The hexagon shape has been verified across increasing normative ranges and provides a critical reference range in which individual results can be compared and tracked. Figure 4 shows brain vital sign changes from healthy baseline to immediate post-concussion to return-to-play in youth ice-hockey athletes as an example of the visual radar plot display.

Two key additional findings emphasized the sensitivity of brain vital sign monitoring: 1) they detected significant residual deficits in basic attention (P300) processing even when athletes were cleared to return to play by existing clinical protocols; and 2) they detected sub-concussive deficits in cognitive processing speed in athletes who did not receive a diagnosed concussion during the season. The latter sub-concussive results have since been

replicated in both US youth ice hockey and football players.[25,40] The latter work in football has been led by Dr. Thayne Munce at Sanford Clinic. Dr. Munce and his team have rapidly expanded brain vital signs to also characterize concussive and subconcussive impairments in mixed martial arts (MMA) athletes.

The initial evidence, therefore, has demonstrated that brain vital signs can be successfully deployed as a rapid, fully automated, and field-tested scientific framework, which has shown strong initial reliability and validity results in both healthy and impaired brain function.[18,24]

ERPs are sensitive to cognitive dysfunction with established test-retest reliability, making them well suited and empirically validated as a sensitive measure on concussion-related impairments.[39,41] Consistent with the results from Fickling et al[38] described above, a review of 13 previous studies evaluating concussed individuals in different settings demonstrated that ERPs have enhanced sensitivity to post-concussive changes in brain function, which are not necessarily detected by neuropsychological tests of symptom-based reporting.[39] The use of ERPs for traumatic brain injury (TBI) has been particularly beneficial in intensive care units of the ease of the method and high reproducibility.[42] The P300 is possibly the most researched ERP for clinical application in brain injury, likely the result of its ability to index attentional processes in the brain.[43,44]

NeuroCatch's investigator-led research trajectory enables partnering with research institutions to gather brain vital signs data in unique neurological populations. In partnership with Drs. Michael Stuart (USA Hockey Team Physician) and Aynsley Smith (Mayo Sports Concussion Research at the Mayo Clinic (Rochester, MN), the NeuroCatch® Platform was deployed in a US-based study designed to demonstrate the value of objective measurements in the diagnosis of concussion and quantification of concussion severity (link). The NeuroCatch® Platform is included in this study as one of several physiological measurements including blood biomarkers and the King-Devick eye movement test. The study results – which demonstrate a relationship between changes in brain vital signs and the number of sub-concussive head impacts received during the season – were published in early 2021.[25] An expanded partnership for NeuroCatch® Platform commercialization through Mayo Clinic sites across the US continues to develop, including moving towards brain fog interventions related to concussion, COVID-19,[26] and age-related cognitive decline.

Beyond studying concussion in adult athletes, an investigator-initiated clinical study, led by Dr. Michael Esser (Head of NeuroTrauma), at the Alberta Children's Hospital is using the NeuroCatch® Platform

to study brain function changes in children with mild traumatic brain injuries (ClinicalTrials.gov NCT03889483). This joint research collaboration uses the NeuroCatch® Platform to explore neurophysiological markers of brain function changes in children with persistent post-concussive syndrome to help researchers shed light on why some children recover faster from traumatic brain injuries than others. Similarly, Dr. Sudhin Shah at Cornell University in New York City has been using NeuroCatch® to track recovery of cognitive function and conscious awareness in survivors of severe brain trauma and has been able to track emergence from coma (Figure 5).

Outside of the clinical research realm, NeuroCatch Inc. currently deploys the NeuroCatch® Platform in several rehabilitation clinics across Canada. In these settings, clients use innovative brain health assessments like the NeuroCatch® Platform to track their progress as they move through various rehabilitation programs.

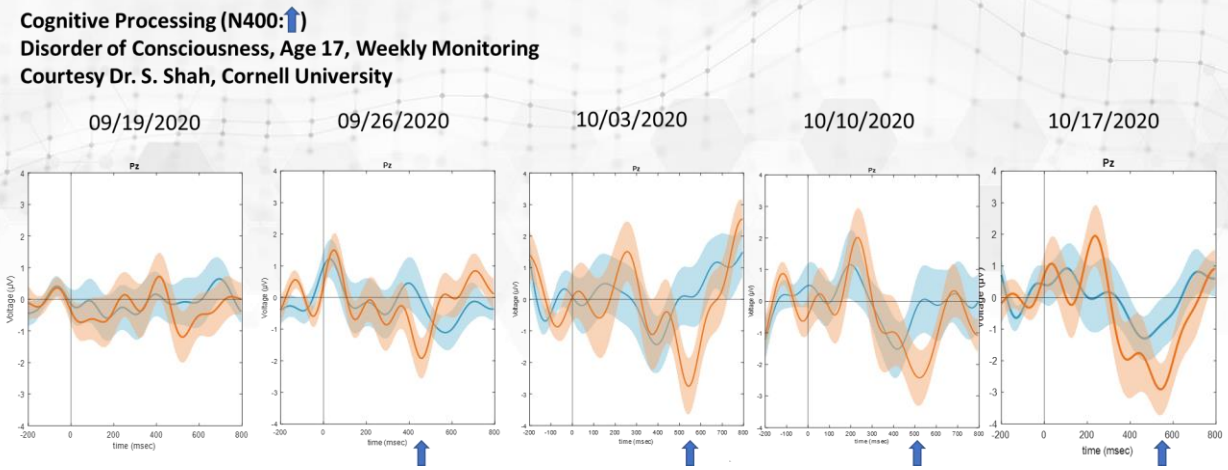

Figure 5: N400 tracks emergence from coma

CLINICAL USE CASE: POST-TRAUMATIC STRESS DISORDER AND MENTAL HEALTH

Post-traumatic stress disorder (**PTSD**) is a chronic, often debilitating condition, and is the direct result of a traumatic event. This condition adversely impacts the emotional, physical, occupational, and social functioning of afflicted individuals. Evidence is accumulating to indicate that health care professionals who are working on the frontline of the COVID-19 pandemic are faced with an ongoing strain on their mental and physical well-being.[45,46] Estimates of acute and post-traumatic

stress in this population are high (56.5 %, 20.2 %), with pooled prevalence of anxiety, depression and sleep problems at 300%, 311%, and 440 %, respectively.[47] Effective ways to treat and manage the wave of PTSD and Mental Health related symptoms because of COVID-19 has become increasingly critical.

The P300 is one of the most widely studied evoked potentials in PTSD. Typically, the literature indicates abnormalities in information processing in individuals diagnosed with PTSD and that differences in ERP features are correlated with the severity of the illness.[48] In 2020, our group completed a case study with Canadian Veteran, Capt. Trevor Greene. In 2006, Capt. Greene suffered a debilitating brain injury from an axe attack while serving in a peace keeping mission in Afghanistan. Although Capt. Greene has shown remarkable recovery since his injury, he had appeared to reach a plateau in his progress. As part of the research study, Capt. Greene underwent a treatment program which paired intensive physical therapy with translingual neuromodulation, and found that, in addition to the objective clinical measures, a range of qualitative improvements were observed that included his own testimonial to a noteworthy reduction in his symptoms of PTSD.[49]

In parallel with motor function improvements, brain vital signs detected significant increases in basic attention (as measured by P300 response amplitude) and cognitive processing (as measured by contextual N400 response amplitude). Quantifying the impact of treatments on symptoms of PTSD will help support the development of evidence-based, impactful, and cost-effective interventions for people with PTSD (Figure 6).

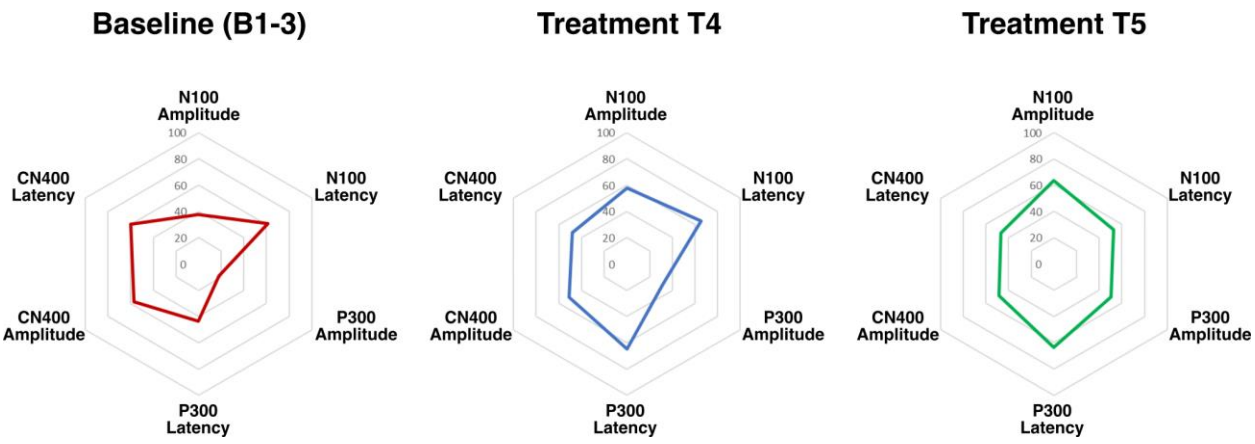

Figure 6: Brain vital signs track improvements in cognitive function and PTSD

CLINICAL USE CASE: DEMENTIA AND ALZHEIMER'S DISEASE

Research has shown that P300 latency increases in individuals with dementia and correlates with the level of the disease.[50] For example, Horvath et al[51] conducted a critical review of current literature on the use of ERP as biomarkers in Mild Cognitive Impairment (**MCI**) and Alzheimer's Disease (**AD**). In this review, P300 latency and amplitude abnormalities are suggested to be sensitive tools for detecting cognitive decline in patients with AD. The authors also noted that P300 changes appeared to be objective and sensitive measures for discriminating subjects with MCI from controls and AD patients; moreover, changes in P300 might be useful in the detection of the transition from MCI to AD. Furthermore, the most common clinical applications of the N400 are in MCI and dementia. Evidence suggests that patients with dementia or MCI may show reduced, absent, or abnormal N400s.[52] These characteristics have been successfully used to predict the conversion of MCI into dementia, specifically being a useful biomarker for the detection and staging of early AD.[51,53] In 2016, our group published a paper demonstrating age-related differences in brain vital signs; in other words, that normal ageing processes were detected.[24]

In partnership with Dr. Frank Knoefel at the Bruyère Research Institute (Ottawa, ON), an investigator-initiated study using the NeuroCatch® Platform is currently assessing whether the conversion from mild cognitive impairment to dementia in older adults can be predicted by these ERPs (ClinicalTrials.gov NCT03676881). This study focuses on brain vital sign monitoring in dementia to identify objective brainwave markers that can potentially help optimize treatment decisions. This work has been complemented by on-going Simon Fraser University brain vital sign research in cognitive impairment and dementia within the seniors' care home Laurel Place, demonstrating that brain vital signs technology can be feasibly applied in studying older residents in long-term care.[54]

Like other vital signs, NeuroCatch® Platform metrics are enhanced with reference values and essential response characteristics (e.g., typical amplitudes and latencies). With this in mind, we have begun a clinical study in which the primary objective is to build a reference interval database and quantify the typical distribution of N100, P300, and N400 measurements elicited and acquired using NeuroCatch® Platform, across the lifespan.

CLINICAL USE CASE: BRAIN PERFORMANCE AND HUMAN OPTIMIZATION

Beyond atypical brainwave responses due to neurological impairments, on the other end of the typical-atypical response spectrum lies human brain optimization. Our group investigated whether neuromodulation paired with cognitive skills training would significantly impact cognitive processing, as measured by brain vital signs in healthy individuals. The analysis concentrated on N400 response amplitudes and latencies as an indicator of high-level cognitive processing. Results demonstrated that neurostimulation led to a sustained N400 response during cognitive skills training, suggesting differential learning effects due to neuromodulation, consistent with increased attention and cognitive vigilance.[31]

Forms of cognitive enhancement, such as optimizing working memory, may have applications for demanding cognitive workload tasks. The potential to measure the enhancement of cognitive skills has widespread implications, for example, in the context of maximizing military and athlete performance. One cognitive training study demonstrated the potential to improve shooting performance through inhibitory control training.[55] Future research studies using the NeuroCatch® Platform aim to explore the ability of the neurostimulation to enhance normal cognitive function and optimize neurological function with Canadian Special Operations Forces.

SUMMARY

The value of the NeuroCatch® Platform comes from the critically important need for an objective, sensitive, physiological measurement of brain health that is also expected to be practically implementable at point-of-care. Current evaluations of brain health rely largely on structural imaging, behavioural cognitive screening, and/or neuropsychological assessments. While all functional neuroimaging technologies play a role, portable and cost-effective technologies, such as EEG, may be able to provide accessible, practical and economical measures of brain function at point-of-care.

This research is built on the recent advances of EEG technology. For almost a century, EEG has made it possible to non-invasively record the brain's electrical activity. While EEG is routinely used clinically for several neurological conditions, its rich and complex physiological data remains largely explored within the depths of a research laboratory. There is a major gap in commercialization and clinical accessibility of breakthrough applications of EEG. The rapid engineering of portable EEG hardware, together with

advanced analytic capabilities have made it possible to enable access to the richness of EEG.

HealthTech Connex is striving towards worldwide accessibility to brain vital sign science through the development of the NeuroCatch® Platform via its subsidiary NeuroCatch Inc. ERPs are clinically useful for a variety neurological conditions[56] – including concussion, PTSD, and dementia – because:

1) ERPs are non-invasive
2) ERPs can provide information about the timing of events during brain activity
3) The scalp distribution of ERP abnormalities may consent to the formulation of hypotheses about abnormally functioning brain regions
4) ERPs allow for monitoring during recovery

The NeuroCatch® Platform provides a rapid and reliable measurement of ERPs, derived from EEG. At the user level, a tool like this could inform the treatment trajectory of many neurological conditions and monitor the optimization of brain health. At the healthcare practitioner level, a quick, easily operational, and less expensive method to monitor intervention could support practitioners and provide more effective patient care. Finally, at the system level, the potential for significant cost savings and improved patient tracking may benefit intervention precision. With a physiological measuring stick of brain function available, everyone can be empowered to maximize brain health.

GLOSSARY OF TECHNICAL TERMS

Alzheimer's Disease (**AD**): A chronic neurodegenerative disease that usually starts slowly and gradually worsens over time, with increasing impairment in learning and memory. It is the cause of 60–70% of cases of dementia.

Electroencephalography (**EEG**): A monitoring method to record electrical activity of the brain.

Event-related potentials (**ERPs**): Very small voltages generated in the brain as a response to specific sensory, cognitive, or motor events, such as listening to an auditory tone or spoken word.

- The **N100**: This ERP represents the acknowledgement by the brain that information has entered auditory systems and indexes auditory processing.
- The **P300**: This ERP indexes basic attentional processing; specifically, the discrimination of one event (e.g., a deviant sound or tone) from another (a standard tone).
- The **N400**: This ERP indexes one of the highest-order cognitive functions: language (semantic speech) processing.

Mild Cognitive Impairment (**MCI**): a neurological disorder which involves cognitive impairments beyond those expected based on an individual's age and education. A person with MCI is at an increased risk of developing Alzheimer's or another dementia.

Post-traumatic stress disorder (**PTSD**): A mental illness that can develop after a person is exposed to a traumatic event.

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