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Towards a practical and accessible measure of brain vital signs: The NeuroCatch^{TM} Platform

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An unmet need for an objective, physiological measurement of brain function

Brain disorders directly impact 1 in 3 Canadians (www.braincanada.ca). Yet, healthcare lacks suitable instruments to measure healthy brain function versus dysfunction in order to guide treatment and monitor recovery. Current assessments for screening brain health and functional status rely heavily on subjective reports. Typical examples include the Glasgow Coma Scale (used to evaluate level of conscious awareness following brain injury[1,2]) 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%,[3,4] and results are often confounded by interrater variability and lack of sensitivity to mild changes.[5] In the same vein, 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, and are restricted by limitations in communication and motor movement.[6–12] Many of these subjective measures, therefore, are susceptible to extraneous influences and have inherent flaws.

An important gap in healthcare exists currently: 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 extensively in research settings.[3,13] Event-related potentials (**ERPs**), measured by means of electroencephalography (**EEG**), are well characterized in the research literature[14] as a physiological measure of brain function, but the transfer of this technology to clinical settings and the frontline of healthcare has been limited to date.

ERPs are 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.[15] As early as the 1930's, ERPs have been extensively studied as indicators of brain function, from low-level sensory to higher-level cognitive processing.[14] Over the past 25 years, our group as led the development of clinical ERP applications.[6–11,16–19] In recent years, integrating ERPs into a clinical setting has focused on developing rapid, automated approaches in order to successfully use key ERPs that can be robustly recorded at an individual level. These signals can be recorded with EEG technology using minimal, non-invasive scalp electrodes.

While familiar to many, the untapped potential and economical advantage of EEG has historically been restricted to specialized laboratory settings.[13] 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.[20,21] As a direct result of advances in EEG technology, it is now possible to move towards creating a brain vital sign framework and viewing brain vital signs as impacting brain health in the same way that heart vital signs impact heart health.

ERP signals can be recorded with EEG technology using minimal, non-invasive scalp electrodes

A practical and accessible measure of brain vital signs

Routinely checking vitals 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 have yet existed for the brain – arguably the most important organ of all.

Recently, university researchers developed a framework to translate key ERPs into practical and accessible brain vital signs.[22] 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 adult individuals;
(4) Easily communicated and accessible to all healthcare practitioners;
(5) Set against reference value ranges of typical response characteristics.

Researchers developed a framework to translate key ERPs into practical and accessible brain vital signs

This brain vital signs framework achieved significant impact in the highly regarded *Frontiers of Neuroscience* journal - receiving the most attention in the journal's history (receiving more views than 95% of all *Frontiers* articles, accessed globally by >13,750 readers, impact factor: 3.877). 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., Evoked Potentials on Answers.com; *Event- related potentials: A methods handbook*; and *Psychophysiology: Human Behavioural and Physiological Response*). Earlier commercialization of this concept won "Top New Medical Technology" at Life Sciences Alley (2012) and the *Wall Street Journal's* Global Technology Start-up Showcase (2015), among others.

In early 2019, the NeuroCatch™ Platform was cleared by Health Canada as a Class II medical device (MDL 102616) and is working towards this scientific framework. NeuroCatch Inc. is bringing this technology platform to the global marketplace for the first time.

Brain vital signs: the new science for analyzing brainwaves

To begin developing brain vital signs, three of the most well-validated[23] ERPs were selected: the N100 (linked to auditory sensation), P300 (linked to basic attention), and the N400 (linked to semantic speech processing). These ERPs were validated across a large sample of healthy individuals and clinically applied in neurological status assessment.[16] ERPs are elicited by listening to stimulus sounds and are described according to latency (milliseconds) and amplitude (microvolts). The NeuroCatch™ Platform uses a quick 6-minute audio sequence of tones and words to evoke these ERPs (Figure 1).

The NeuroCatch™ Platform uses a 6-minute audio sequence of sounds and words to elicit ERPs

The N100 occurs about 100ms after a tone is played and represents the acknowledgement by the brain that information has entered auditory processing systems.[24]

The P300 occurs about 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).[25]

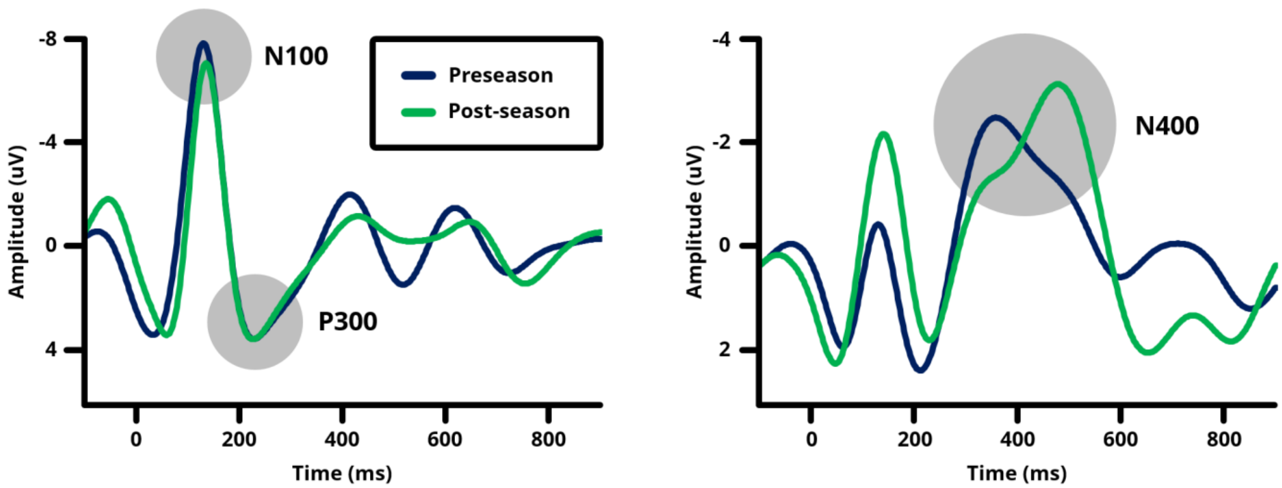

Figure 1: Typical EEG responses showing sub-concussive cognitive processing impairments in hockey players with pre- and post-season brain vital sign monitoring.

On the left: Responses to auditory tone sequences. The N100 marks information entering the auditory system, while the P300 marks the classification of a deviant tone. On the right: Typical responses to spoken word pair sequences using EEG hardware. Incongruent word pairs demonstrate increased N400 amplitude, indicating elevated cognitive and language processing. Post-season N400 response latency was significantly delayed, reflecting sub-concussive impacts on brain function.

The N400 peaks at about 400ms after a word is played. This response occurs when unexpected or incongruent word pairs are detected (e.g., when hearing 'The pizza was too hot to … sing"), therefore indexing one of the highest-order cognitive functions: language processing.[19,26,27]

Importantly, ERPs have been extensively studied in the scientific literature. At the time of writing, a PubMed search of "event related potentials" returned 139,412 peer-reviewed publications dating back to 1946, with the first reported evoked response dating back to 1934[28] and nearly 4000 new published studies in the last year alone, representing a robust scientific foundation on which to commercialize this technology.

Equally important, engineering advances have enabled the development of many portable EEG systems, now making it possible to move this technology from a controlled laboratory or hospital setting to any desired point-of-care setting for rapid, economical brainwave recording.[29] Consumers worldwide can now purchase EEG devices and

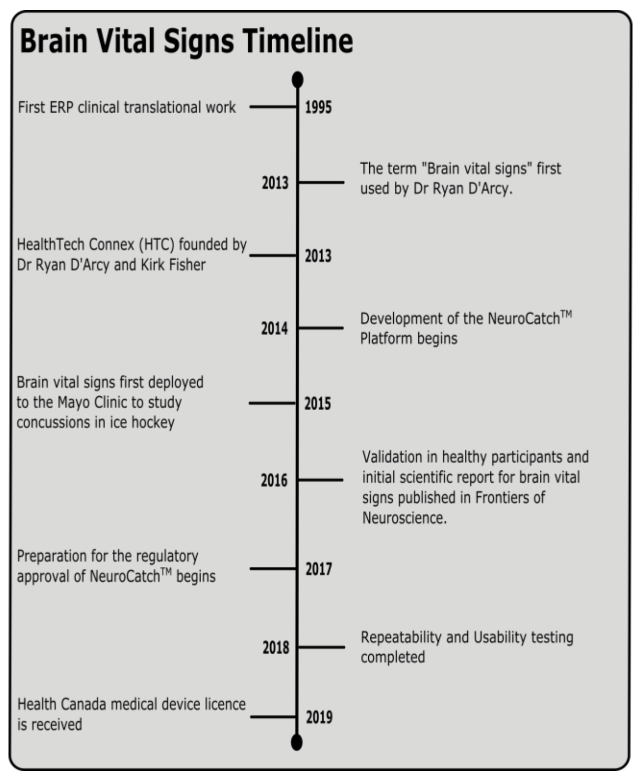

Figure 2: The timeline of brain vital signs science and the development of the NeuroCatch™ Platform device to date

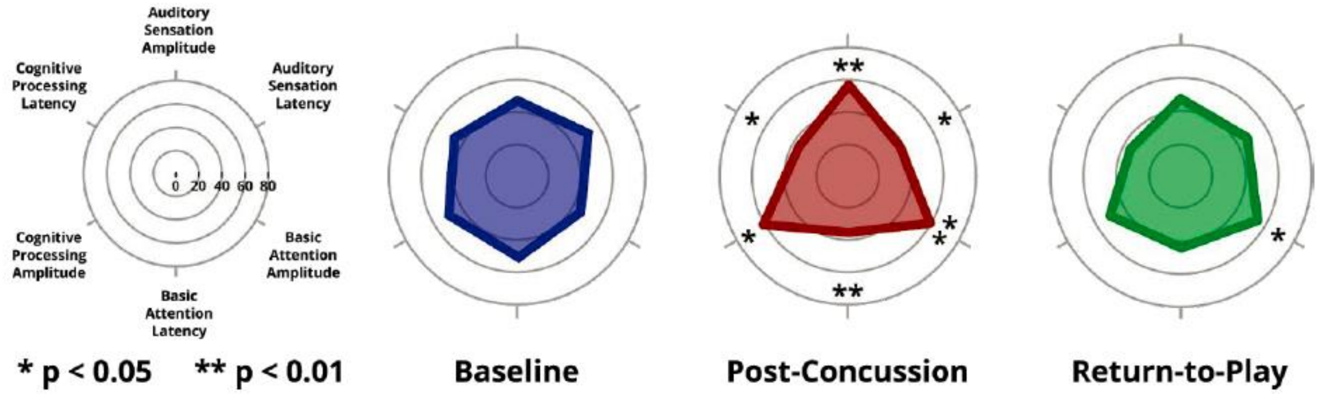

Figure 3: Changes in ERP latencies and amplitudes after concussion[30]

technologies at their local electronics stores or over the internet, such as the Muse™ device or HealthTech Connex's 5-star rated Brain Power Score™. Integrated within these new evolutions, the NeuroCatch™ Platform technology has systematically moved through a planned program of design, development, validation, and clinical testing, summarized in Figure 2.

Initial Development: Critical Science and Clinical Validation through University Research

Brain vital signs Research & Development (R&D) dates back more than 20 years. With more than 25 international, peer reviewed scientific papers published (empirical, invited reviews and editorials), the medical equity for brain vital signs has been well established. In addition, 8 patents and provisional patent applications, together with technical reports and book chapters, highlight the clinical application of ERPs. The joint university-industry brain vital signs R&D team has garnered all major prestigious competitive funding awards in Canada (Canadian Institutes of Health Research, Canada Foundation for Innovation, Mitacs, Natural Sciences and Engineering Research Council, etc.) and includes more than 12 highly qualified research personnel (e.g., PhD and Master degrees). The team is led by Dr. R. D'Arcy, who is a BC Leadership Chair and full tenured Professor at Simon Fraser University and Surrey Memorial Hospital.

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[22] and in collaboration with partners at Simon Fraser University and Surrey Memorial Hospital, the brain vital signs technology was first deployed to the Mayo clinic in a multi-year research program examining concussions in ice hockey.

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, return-to-play, and recovery (Figure 3). Importantly, brain vital signs changes in concussion also appear 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 3).[30] These brain vital sign changes were fully consistent with previous literature showing that ERPs have enhanced sensitivity to post-concussive changes in brain function, which are not necessarily detected by neuropsychological tests of symptom-based reporting.[31] Two key additional findings emphasized the sensitivity of brain vital sign monitoring: 1) they detected significant residual deficits in basic attention processing 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 US junior football players.[33]

Brain vital signs has the potential to be deployed as an easy-to-use technology with intuitive interfacing, requiring no expertise in EEG

The initial evidence, therefore, has demonstrated that brain vital signs can be successfully deployed as a rapid, fully automated, and field-tested technology, which has shown strong initial reliability and validity results in both healthy and impaired brain function testing. [16,22] Indeed, a recent study in the *Journal of Translational Medicine* linked brain vital signs from the N400 to the established cognitive neuroanatomical framework that has been fully characterized within the scientific literature.[32]

Current Industry Developments: NeuroCatch™ Platform Commercialization

NeuroCatch Inc., a wholly owned subsidiary of HealthTech Connex, was established to commercialize brain vital sign science through technology product development of the NeuroCatch™ Platform. The NeuroCatch™ Platform obtained its Health Canada medical device licence on March 22, 2019 (MDL 102616). The currently deployed NeuroCatch™ Platform runs in approximately 6-minutes and is fully automated.

HealthTech Connex itself 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. With the Lark Group as its parent company, HealthTech Connex is an award-winning, high tech start-up in hypergrowth mode, with brain technology products in the marketplace and active revenue generation ($1.2m in 2017). HealthTech Connex was recently recognized internationally by Brainnovations, as well as an Emerging Rocket company on BC's Ready to Rocket list. With the NeuroCatch™ Platform as the anticipated premier technology product once approved for commercial distribution, HealthTech Connex has successfully expanded to include strategic neurotechnology partnerships in both products and services globally.

The NeuroCatch™ Platform obtained its Health Canada medical device licence in March 2019

NeuroCatch Inc. deploys the NeuroCatch™ Platform throughout Canada's Heuro™ neurological rehabilitation clinics. Heuro™ clinics offer comprehensive, client-focused care plans that include innovative treatments and technologies to promote neuroplastic healing, including the PoNS™ portable neuromodulation stimulator. The Heuro™ Program featuring PoNS™ Treatment is specifically designed for clients who experience chronic balance deficits due to mild-to-moderate traumatic brain injury. In addition to providing leading evidence-based therapies, Heuro™ clinics across Canada employ innovative brain health assessments to track client progress as they move through the Heuro™ Program.

Future Developments

Further clinical evaluations of the NeuroCatch™ Platform are underway for assessment of concussion and traumatic brain injury, as well as other neurological indications, alongside planned expansion to global markets such as the United States, Europe and Australia. HealthTech Connex is an R&D company and has a full product development roadmap plan for the NeuroCatch™ Platform through its subsidiary NeuroCatch Inc.

Current research and testing of the NeuroCatch™ Platform includes:

- *Creating a reference value database in order to quantify NeuroCatch™ response ranges from adolescents to elderly individuals (ClinicalTrials.gov Identifier: NCT03835962)*

Like other vital signs, NeuroCatch™ Platform metrics should have 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.

- *Investigator-based research*

NeuroCatch Inc.'s planned investigator-led research trajectory enables partnering with research institutions in order to gather data in unique neurological populations. This work is vital to underpin future commercialization plans for the NeuroCatch™ Platform.

In partnership with ABI Wellness, NeuroCatch Inc. has launched a clinical trial aiming to assess neurophysiological changes using the NeuroCatch™ Platform in individuals with symptoms of chronic traumatic brain injury (ClinicalTrials.gov Identifier: NCT03438851). This study of up to 50 participants could help further shed light on whether neurophysiological changes can be detected alongside, or before, functional improvements for individuals with traumatic brain injury.

In partnership with the Mayo Clinic and led by Drs. Michael Stuart and Aynsley Smith, the NeuroCatch™ Platform is currently deployed in a US-based study designed to demonstrate the value of objective measurements in the diagnosis of concussion and quantification of concussion severity (https://mayocl.in/2E9sAtS). The NeuroCatch™ Platform is included in this study as a component of several physiological measurements including blood biomarkers and the King-Devick eye movement test.

An investigator-initiated clinical study 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 with Dr. Michael Esser uses the NeuroCatch™ Platform to explore neurophysiological markers of brain function changes in children in order to help researchers shed light on why some children recover faster from traumatic brain injuries than others.

In partnership with the Bruyère Research Institute and led by investigator Dr. Frank Knoefel, an additional study is designed to assess whether the conversion from mild cognitive impairment to dementia in seniors can be predicted by ERPs as captured by the NeuroCatch™ Platform (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 SFU brain vital sign research in cognitive impairment and dementia within the seniors care home Laurel Place.

Finally, future longitudinal studies will establish individual functional "baselines" of brain status prior to brain injury or disease, in order to provide evidence for effective long-term monitoring of brain functional changes.

Summary

The value of the NeuroCatch™ Platform comes from the critically important need for an objective, 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 of breakthrough clinical applications in EEG. The rapid engineering of portable EEG devices together with computer science data analysis advances have now made it possible to enable access to the richness of EEG, making EEG accessible to clinical settings everywhere through this technology.

HealthTech Connex is ensuring worldwide accessibility to brain vital sign science through the development of the NeuroCatch™ Platform via its subsidiary NeuroCatch Inc. The NeuroCatch™ Platform received its medical device licence from Health Canada in March 2019 and is intended for the elicitation, acquisition, analysis, storage, reporting and management of ERP information. It is intended for use by qualified healthcare professionals and clinical staff. Current and future research using the NeuroCatch™ Platform in neurological populations will underpin future commercialization plans for the device.

The NeuroCatch™ Platform provides a rapid and reliable measurement of ERPs, derived from EEG. At the patient level, a tool like this could inform the treatment trajectory of many neurological conditions. 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 treatment precision. With a physiological measuring stick of brain function available, all stakeholders can be empowered to manage brain health.

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