Electrophysiology Biomarkers to Aid in Diagnosis:

Magnetically induced Brain Health Biomarkers

The Brain Health Challenge. 90% of strokes and 35% of dementias have been estimated to be preventable if detected early enough to enable effective medical intervention[1, 2] . For this reason, the American Academy of Neurology has recently recommended routine annual brain health assessment for population 65 years and older[3]. The rational being that routine assessment of high-risk individuals provides an opportunity to improve the detection of early functional brain abnormalities and enable earlier intervention while the disease is still in it's early, abnormal physiological state and before it deteriorates into the late pathological - degenerative state of progression (Fig.1)[4]. However, current diagnostic tools lack the sensitivity and objectivity needed for early and accurate diagnosis, leading to under-diagnosis at extremely late stages that might already be untreatable[5, 6]. Thus, there is an urgent need for a fast, easy-to-use, low-cost, objective, and sensitive test that will aid the diagnosis of the physician. This enormous challenge increases as world population continues to grow due to rise in life span and with it the age-related brain disorders such as Cerebral Small Vessels Disease (CSVD), stroke, mild cognitive impairment (MCI) and dementia, etc. [4, 7].

Electroencephalography (EEG) combined with Transcranial magnetic stimulation have been employed extensively in clinical research to provide a non-invasive, direct and reliable solution for objectively measuring physiological properties of brain function[8, 9] (fig 2).

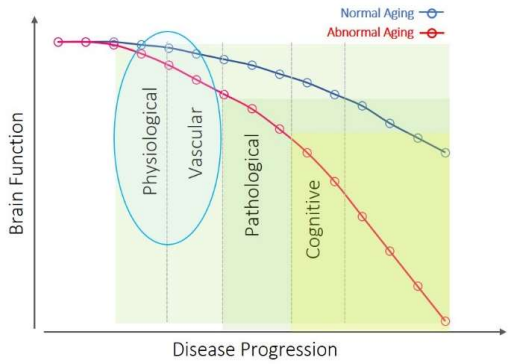

Figure 1. Normal vs. Abnormal decline in brain function duration aging. Routine brain health Assessment will enable the detection of early brain functional abnormalities (caused by physiological and/or vascular changes) and allows earlier intervention before the deterioration into the late stages of cognitive decline and pathological degeneration.

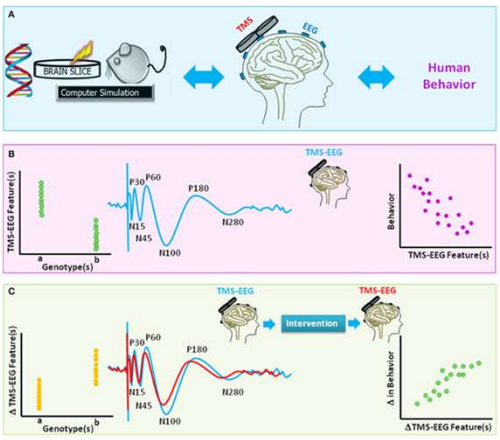

Figure 2: A schematic diagram of translational value of magnetically induced electrophysiology (Adapted from Farzan et 2016): (A) The method of **magnetically induced electrophysiology** provides a means to non-invasively assess the integrity and characteristics of numerous brain circuitries in the intact human brain using. (B) The blue waveform illustrates schematics of typical magnetically induced electrophysiological response (TEP) when suprathreshold single-pulse is applied to the primary motor cortex. Various characteristics of TEP such as amplitude or latency of components [e.g., negativity at latency 15 ms (N15), positivity at latency 30 ms (P30), N45, P60, N100, P180, N280] are highlighted. The scatter plots are schematic illustrations of the link between TMS-EEG features and genetic variations (left panel) or behavior (right). (C) The waveforms highlight change in TEPs for two hypothetical brain states (e.g., before and after an intervention). The scatter plots are schematic illustrations of the link between change in TMS-EEG features and genetic variations (left panel) or change in behavior (right panel).

DELPHI™: The First Objective, Patient-Independent System for Visualization of Brain Health. DELPHI™ provides physicians with real-time objective, highly reproducible, assessment of brain function without the need for subject participation. It is easily integrated into any clinical setting for routine brain health assessment or emergency medicine. DELPHI™ provides physicians with valuable insights into their patient's brains health while saving the healthcare system a significant percent of clinical assessment and diagnosis costs.

DELPHI™ is a CE cleared medical device for brain function and health assessment, aiding physicians in diagnosis by providing direct and objective, brain function biomarkers of early brain degeneration conditions. Using DELPHI™ the physician can perform a differential diagnosis and determine an optimal course of preventive treatment.

DELPHI™ System Principals of Operation. DELPHI™ operates a combination of focused magnetic stimulation and electroencephalography measures with unique algorithms to measure well-characterized physiological properties of brain function in specific brain networks such as cortico-spinal network, fronto-parietal network, inter-hemispheric connections and visual network (fig 3).

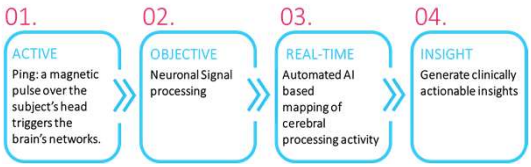

Figure 3: DELPHI™ principals of operation.

Brain Health function Biomarkers. Brain is a highly complexed network composed of large-scale connections and functional hubs that facilitate communication within and across brain structures. Their communication (connectivity) and reactivity can be evaluated utilizing well established and specific biomarkers of TMS evoked potentials (TEPs)[8, 10] and rest EEG. TEP waveforms represent generated neuronal response to specific TMS stimuli. The latency of response reflects brain processing speed and connectivity, while TEP amplitude reflects neuronal recruitment and activation. DELPHI™ measures include: 1) The response latency to stimulation in specific networks such as the cortico-spinal and frontal network which represents network connectivity. 2) The response charge to stimulation in specific networks such as the cortico-spinal and frontal network, which represents network excitability and reactivity. 2) The interhemispheric coherence of evokes response to stimulation 3) Specific network short term plasticity (STP), which reflects the ability of the network to process information and change the inhabitation to excitation balance in accordance with network requirements. 4)Thalamic-generated peak alpha frequency (posterior dominant rhythm). 5) quantitative EEG brain function scoring. DELPHI™ evaluation takes a total of 20 minutes and does not require any patient participation.

TMS Evoked Potential (TEP). TEP is the defined as the EEG pattern of response to a localized magnetic stimulation (figure 4A). TEP in motor areas (M1) indicates changes in motor network connectivity and excitability as reflected in cases of motor dysfunctions, movement disorders and stroke [8, 10]. Changes in TEP response in frontal network areas (dorsal lateral frontal cortex) indicate progression of dementia such as early stages of Alzheimer's disease[11] and neuropsychiatric disorders [12].

Network Short Term Plasticity (STP). DELPHI™ measures of Network STP are obtained by quantifying the changes in the excitation and inhibition component of the TEP response (figure 3B). Regional network STP evaluates the network ability to change the ratio between these components of evoked pattern of response, reflecting the crucial capacity of the network to process information. Normal brain aging is associated with decrease measured STP. Moreover, pathological decrease in STP in specific brain network regions like the Entorhinal cortex, Hippocampus and frontal areas is known to be strongly correlated with early stages of neurodegenerative process and the best correlate with disease progression[13, 14].

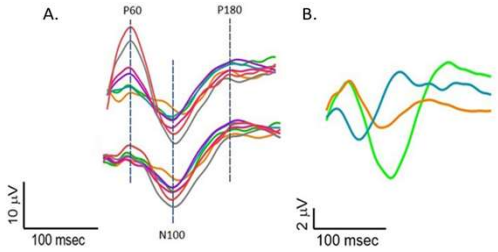

Figure 3: Pattern of TEP response. Evoked response is represented as a collection of time locked amplitudes and latencies (P60,N100,P180). Single pulse response refers to the evoked response to a single TMS pulse in varying intensities (A). Network STP refers to frequency dependent changes in evoked response. High frequency of stimulation evokes excitation of network response while low frequency evokes inhibition of the regional network response (B)[13].

Peak Alpha Frequency (PAF). The most dominant EEG frequency found in the brain is alpha frequency band (8 – 12 Hz) which mostly reflects thalamo-cortical network activity. PAF can therefore be conceptualized as the pacemaker of the brain and is known to be a good measure of information processing capacity [15].

PAF rises from childhood to adolescence, and then decreases slowly with age (11). Regardless of age, individuals with strong working memory abilities have faster PAF compared to inferior memory performers[16]. Abnormally low PAF (< 8 Hz) can be found in patients with cognitive disturbances and dementia (Figure 4). Abnormally slow PAF is correlated with loss of hippocampal volume in many posterior regions of interest in patients with Mild Cognitive Impairments (MCI)[17]. PAF electrophysiology biomarker is used to help identify patients with pre-clinical dementia and monitor patients' overall cognitive capacity.

Quantitative EEG. qEEG pattern of frequency band has been shown to change in specific neurological conditions, it's analysis is a well-established method for distinguishing dementia from pseudo-dementia cases. Moreover, qEEG brain maps provide information relevant to discriminate between specific dementia diagnoses, such as Alzheimer's disease and vascular dementia (Figure 4)[18].

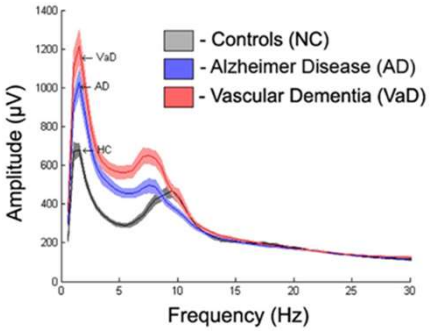

Figure 4. Averaged frequency spectrum discriminates between Normal controls (NC) Alzheimer's (AD) and Vascular Dementia (VaD) [18].

Conclusion. DELPHI™ system is a clinically available, easy-to-use, real-time and affordable device for the evaluation and monitoring of brain health status. DELPHI™ combines well established and completely safe technologies for non-invasive brain stimulation and monitoring. DELPHI™ provides physicians with an accurate direct and objective tool supporting the routine diagnostic process, recognizing early, pre-clinical abnormal aging conditions such as cerebral small vessels disease, dementia or stroke, and perform differential diagnosis.

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