Evaluating the Clinical Utility of a Novel Electroencephalography System for Assessing Perioperative Neurocognition in Older Surgical Patients

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Evaluating the Clinical Utility of a Novel Electroencephalography System for Assessing Perioperative Neurocognition in Older Surgical Patients

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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“If I have seen further, it is by standing on the shoulders of giants.” – Isaac Newton

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Abstract

EVALUATING THE CLINICAL UTILITY OF A NOVEL ELECTROENCEPHALOGRAPHY SYSTEM FOR ASSESSING PERIOPERATIVE NEUROCOGNITION IN OLDER SURGICAL PATIENTS

L. Harold Barnwell, III, PhD, DNAP, CRNA

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2021

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Postoperative delirium (POD) is a public health and research priority (American Society of Anesthesiologists, 2019). POD is a risk factor for long-term neurocognitive decline, and the rate of decline is directly proportional to the severity of POD (Vasunilashorn et al., 2018). Baseline cognitive function is a strong, independent predictor for POD (Culley et al., 2017). The International Perioperative Neurotoxicity Working Group recommends baseline cognitive function be assessed for older patients prior to surgery and anesthesia (Berger, et al., 2018). Perioperative cognitive screening tools trialed in anesthesia are not routinely incorporated into clinical practice related to validity, reliability, or practicality problems (Berger, et al., 2018). The ideal perioperative cognitive screening tool would be rapid, easily-administrable, valid, reliable, automatically scored, void of language, cultural, and education bias and cost-efficient (Axley & Schenning, 2015). No such tool has been identified to date. This study, guided by Donabedian’s theoretical model, evaluated the utility of a novel point-of-care (POC) electroencephalography
(EEG) system, WAVi Medical™ (Boulder, CO), for the perioperative neurocognitive assessment of older surgical patients. This study conducted a secondary analysis of data from the “Perioperative Brain Health” – IRB HM20019839 study. The “Perioperative Brain Health” study is an ongoing study collecting both pre- and postoperative questionnaire-based neurocognitive assessments alongside WAVi-derived P300 auditory evoked potentials. Data was analyzed using regression and analysis of variance. The WAVi Medical™ system may one day offer anesthesia providers a novel neurocognitive assessment tool for predicting, identifying, and tracking perioperative neurocognitive disorders in older surgical patients.

Keywords: perioperative neurocognitive disorders, postoperative delirium, older surgical patients, geriatrics, electroencephalography, EEG, auditory evoked potentials, anesthesia
Chapter 1: Introduction

Study and Chapter Overview

The purpose of this study was to explore baseline and postoperative neurocognitive characteristics that may help to establish novel predictive and trend metrics for perioperative neurocognitive assessment in older surgical patients. This study is important because neurobiomarkers obtainable with a new point-of-care (POC) electroencephalography (EEG) brain assessment device, WAVi Medical™ (Boulder, CO), might provide anesthesia providers with a more detailed perioperative assessment of a patient’s brain, the primary target of anesthesia, than is currently available with questionnaire-based assessment tools (e.g., Montreal Cognitive Assessment (MoCA), Mini-Cog®, Confusion Assessment Method (CAM)). This study assessed the potential for P300 auditory evoked potentials (AEPs) obtained using the WAVi Medical™ cognitive screening system to identify and track perioperative brain health in older surgical patients to fill a gap in the literature in the quest to discover the ideal perioperative cognitive screening tool.

The study is significant because, long-term, such a device may assist researchers and clinicians in determining neurobiomarkers that could be utilized to develop a perioperative brain health protection protocol to reduce the incidence and/or severity of perioperative neurocognitive disorders, such as postoperative delirium (POD), in older surgical patients. Patients experiencing POD present with varying degrees of confusion and inattention. This cognitive state is associated with diminished recovery, increased length of stay, higher rates of morbidity and mortality, and
escalated health care costs (Saczenski et al., 2012; Koster et al., 2012; Hshieh et al., 2017; Sprung et al., 2017; Aranake-Chrisinger & Avidan, 2017).

Chapter one offers a succinct background on POD and perioperative neurocognitive assessment. Concise summaries of the study’s purpose and significance are provided. Brief overviews of the study’s theoretical framework and methodology are presented. The chapter concludes with the organization of remaining chapters.

Background

POD, a state of disorganized thinking and inattention, complicates the postoperative recovery of a significant number of surgical patients age 60 years and older (American Geriatrics Society, 2015). Patients suffering POD may present as sluggish or restless with impaired cognitive function for up to one week following surgery and anesthesia (American Geriatrics Society, 2015). A subset of patients, 12-21%, who suffer POD following non-cardiac surgery show signs of a postoperative neurocognitive disorder that lasts up to 3 months and 10% demonstrate reduced cognitive function one to two years later (Abildstrom et al., 2000; Evered and Silbert, 2018). Pediatric and young adult patients may experience emergence delirium for approximately thirty minutes following surgery and anesthesia. However, as patients advance in age over the age of 60 years, they are more likely to experience POD and associated long term cognitive sequelae than are pediatric or young adult patients (Sanders et al., 2011). As such, this study focused on older adults.

Over 30 POD risk factors have been identified making preoperative prediction challenging across a wide variety of surgical procedures. POD is problematic because it distresses patients, loved ones, and caregivers and is associated with: 1) diminished functional recovery, 2) prolonged length of stay, 3) increased care dependency, 4) increased long-term
morbidity & mortality, and 5) increased health-care costs (Wu et al., 2019). For these reasons, the American Society of Anesthesiologists’ (ASA) *Perioperative Brain Health Initiative* endorses identification of patients at-risk for POD and advocates for research to discover novel POD identification, mitigation, and prevention strategies (American Society of Anesthesiologists, 2019).

**Research Problem**

Anesthesia providers perform a thorough preoperative assessment of cardiovascular and respiratory function by conducting a detailed history and physical examination (e.g. assessing metabolic equivalency to task (METs), auscultating the heart and lungs, and reviewing pertinent laboratory values). However, limited assessment of anesthesia’s primary target, the brain, is routinely performed beyond assessing orientation to person, place, time, and task (i.e., alert and oriented times four (A&O x 4)). Crosby et al. (2011) lamented this problem:

…that we currently make no effort to identify [older patients with a vulnerable brain state] preoperatively is an embarrassing state of affairs considering that the brain is a principal target of general anesthetic agents, the field of anesthesiology champions thorough preoperative evaluation, and perioperative cognitive morbidity in the elderly is so common and costly (p. 1267).

The problem is that no easily-administrable, rapid, reliable, highly sensitive and specific assessment of neurocognitive function currently exists to preoperatively identify patients either with or at risk for developing a perioperative neurocognitive disorder.

A POC EEG device capable of rapidly performing easily-administrable, reliable, sensitive, and specific neurocognitive assessments at the bedside might enable anesthesia providers to better assess baseline neurocognitive function in older surgical patients prior to
surgery and anesthesia. Objective assessments derived from such a device may also detect neurocognitive changes (e.g., mild or even subsyndromal cognitive impairments) that are currently missed in a subset of patients by clinically utilized cognitive assessment tools (e.g., MoCA, Mini-Cog©, and CAM) as well as track the progression of patients’ cognitive status to determine if, and when, neurocognitive function is improving or worsening perioperatively.

**Gap in the Literature**

The WAVi Medical™ system is a novel U.S. Food and Drug Administration (FDA)-cleared POC EEG hardware and software system for rapidly assessing auditory evoked potentials (AEPs) to assess cognitive function. AEPs, also known as auditory event-related response tests, assess the brain’s response to a novel stimulus and are conducted using an oddball paradigm (van Dinteren et al., 2014). An oddball paradigm consists of the presentation of a random assortment of auditory stimuli (e.g., combination of high- and low-pitched tones). During AEP testing, healthy brains process and respond to a novel stimulus (e.g., high-pitched tones) differently than when presented with a series of background stimuli (e.g., low-pitched tones). Variation in the brain’s response to a background versus novel auditory stimulus is identifiable in the amplitude and latency of EEG waveforms. Brain speed and efficiency are associated with signal latency (i.e., the delay in response, measured in milliseconds) on EEG. Brain power and cognitive resources are associated with signal amplitude (i.e., the power of a response, measured in microvolts).

Changes in the amplitude and latency of the P300 waveform are associated with altered neurocognitive states (Polich, 2004; Sur & Sinha, 2009; Clayton et al. 2020). Specifically, reduced P300 amplitude is indicative of a state of neurobiological vulnerability (Sur & Sinha, 2009). P300 event-related evoked response tests can be used as a neurophysiological marker for
even mild neurocognitive disorders (Levada et al., 2016). Yener et al. (2013) demonstrated that evoked potential tests can be used to detect mild cognitive impairment. Parra et al. (2012) reported that P300 is a “very useful method for the preclinical assessment of [Alzheimer’s disease], particularly in populations with low socioeconomic and education levels (p. 1).” AEP testing may have utility for assessing and tracking patients’ neurocognitive function in the perioperative setting.

The WAVi Medical™ system is a unique device that utilizes innovative saline soaked fabric electrodes, eSocs™, to conduct and capture the brain’s electrical activity and an integrated artifact detection software system that enhances test-retest and inter-rater reliability when conducting POC EEG-based assessments. These system characteristics improve the clinical practicality of rapidly performing EEG-based neurocognitive assessments. The WAVi Medical™ system was successfully used to assess baseline cognitive function and track changes over time in individuals with traumatic brain injury (Grover et al., 2017; Clayton et al., 2020). The WAVi Medical™ system is currently being used as a neurocognitive assessment tool in a National Institutes of Health (NIH)-funded chronic pain study (National Institutes of Health, 2018). The WAVi Medical™ system is also being utilized to measure onset and progression of cognitive decline in preclinical Alzheimer’s patients at the University of Texas at Dallas (Clinicaltrials.gov, 2018). The current study is innovative in that the WAVi Medical™ system has never been evaluated as a neurocognitive assessment tool for perioperative neurocognitive disorders.

**Theoretical Framework**

The study implements Donabedian’s theoretical model to guide measurement of improvement in quality of care (Donabedian, 2005). The three primary constructs used to guide
this research were: structure (e.g., attributes of a patient, system, or provider), process (i.e., current best practice versus potential new intervention), and outcome (i.e., the end result of improvement work). Structure refers to the physical and organizational characteristics where healthcare occurs. In this study, structure references the perioperative setting (i.e., the preoperative assessment, communication, and education clinic (PACE)), preoperative holding area, operating room, post anesthesia care unit, and patient follow-up). Process refers to the care provided, and outcome refers to the effect of the intervention. The process-outcome being considered is the potential utility of P300 neurobiomarkers versus best medical practice (e.g., Montreal Cognitive Assessment (MoCA)) to identify and track perioperative neurocognition in older surgical patients.

**Purpose Statement**

The purpose of this study was to explore baseline and postoperative neurocognitive characteristics that may help to establish novel predictive and trend metrics for perioperative neurocognitive assessment in older surgical patients. These neurobiomarkers might enable a more detailed perioperative assessment of a patient’s brain state than do questionnaire-based assessment tools. Long-term, these assessments may assist the development of a perioperative brain health protection protocol to reduce the incidence and/or severity of perioperative neurocognitive disorders in older surgical patients.

**Research Method**

To evaluate the utility of P300 AEPs for assessing and tracking perioperative brain health in older surgical patients, the following methodology was used. The study employed a non-experimental *ex post facto* secondary data analysis design to retrospectively: 1) compare participants’ baseline P300 AEPs to MoCA scores before surgery and anesthesia and 2) evaluate
for group differences in pre- to postoperative P300 AEP change scores between participants who received two or more potentially neuroprotective multimodal anesthetic adjunct medications versus those who did not.

Data was analyzed using a combination of regression and analysis of variance (ANOVA). This study used regression to gauge whether P300 AEPs are predictive of participants’ MoCA scores. This study used ANOVA to assess for group differences in change scores (i.e., the change from preoperative baseline to postoperative scores) between participants who received two or more potentially neuroprotective multimodal anesthetic agents and participants who did not.

Data Source

Data for this study was extracted from the VCU/VCUHS research electronic data capture (REDCap®) database: “Perioperative Brian Health” – PID 22988. Data in this database was collected using a longitudinal, repeated measures design to conduct a prospective observational trial with a set of pretests and multi-observation post-tests. Preoperative baseline neurocognitive assessments were completed using the WAVi Medical™ software and hardware system and MoCA (see Appendix B). Figure 1 depicts the WAVi Medical™ neurocognitive assessment platform.

Figure 1

*The WAVi Medical™ Neurocognitive Assessment Platform*
Following surgery and anesthesia, participants underwent postoperative neurocognitive assessments using the WAViMed™ system, Mini-Cog®, and CAM. At the time of this study’s analysis, the primary study’s database contained 20 participant records. The impact of this study’s sample size on statistical conclusion validity was noted and accepted as this was a proof-of-concept study.

**Research Question, Specific Aims, and Hypotheses**

This study’s research question was: Could P300 AEPs obtained using the WAVi Medical™ system potentially enhance perioperative brain health assessment and provide neurobiomarkers that aid in the development of perioperative brain health protection protocols for older surgical patients?

Specific Aim #1: Evaluate the ability of participants’ preoperative baseline P300 amplitude (i.e., brain power) and P300 latency (i.e., brain speed) to predict participants’ cognitive function. This study used regression to understand whether auditory P300 amplitude (in microvolts) and auditory P300 latency (in milliseconds) predict cognitive function among older surgical patients as assessed by MoCA. Each variable was considered independently as they measure two separate constructs of neurocognition, namely cognitive resources (i.e., brain power) and cognitive efficiency (i.e., brain speed).

Hypothesis #1: Lower P300 amplitude will be predictive of lower MoCA scores.

Hypothesis #2: Higher P300 latency will be predictive of lower MoCA scores.

Specific Aim #2: Evaluate for group differences in pre- to postoperative P300 AEP change scores (i.e., amplitude (in microvolts) and latency (in milliseconds)) between participants who received two or more potentially neuroprotective multimodal anesthetic
adjunct medications (i.e., magnesium, lidocaine, and/or ketamine) versus those who did not.

**Hypothesis #3:** Participants who received two or more potentially neuroprotective multimodal anesthetic agents will demonstrate a larger positive change in their P300 amplitude, measured as a pre- to postoperative change score in microvolts.

**Hypothesis #4:** Participants who received two or more potentially neuroprotective multimodal anesthetic agents will demonstrate a smaller degree of prolongation in their P300 latency relative to their baseline, measured as a pre- to postoperative change score in milliseconds.

**Study Significance**

This study was important because it demonstrated that the WAVi MedicalTM system could be employed as a research tool for neurocognitive assessment within the perioperative clinical setting. Pending further investigation, the WAVi MedicalTM system may one day enable anesthesia providers to: 1) perform a rapid, valid, and reliable neurocognitive assessment that is more sensitive and specific than questionnaire-based cognitive screening tools (e.g., MoCA, Mini-Cog©, and CAM), 2) predict POD risk and stratify patients into risk categories, 3) detect mild cognitive impairments currently missed by brief cognitive screening tools (e.g., MoCA, Mini-Cog©, and CAM), and 4) objectively track the progression of postoperative cognitive changes over time. This contribution is significant because a device capable of rapidly and reliably predicting, identifying, and tracking perioperative neurocognitive disorders (e.g., POD) may enable anesthesia providers to develop and evaluate the effectiveness of perioperative brain health protection protocols, clinical pathways, and pharmacologic strategies that reduce the incidence and severity of these disorders in older surgical patients. These processes could
potentially improve patient outcomes and reduce care costs associated with perioperative neurocognitive disorders (Axley & Schenning, 2015).

**Summary of Key Points**

Neurocognitive decline associated with surgery and anesthesia complicates the recovery of a subset of older surgical patients (American Geriatrics Society, 2015). POD, the first acute event of postoperative neurocognitive impairment, is a public health and research priority of the American Society of Anesthesiologists (ASA), American College of Surgeons, American Geriatrics Society, American Heart Association, Alzheimer’s Association, and American Association of Retired Persons (Mahanna-Gabrielli et al., 2019). The precise mechanism causing POD has yet to be elucidated and is likely multifactorial (Wu et al., 2019). What is known is that baseline cognitive function is a strong, independent predictor for POD in older surgical patients (Culley et al., 2017). POD is a risk factor for long-term neurocognitive decline, and the rate of decline is directly proportional the severity of POD (Vasunilashorn et al., 2018).

The International Perioperative Neurotoxicity Working Group recommends that baseline cognitive function be assessed in older surgical patients prior to surgery and anesthesia (Berger, et al., 2018). Several cognitive screening tools have been trialed in anesthesia practice (e.g., MoCA, Mini-Cog®, and Mini-Mental State Exam (MMSE)) (Berger, et al., 2018). However, none of these tools have been widely adopted into routine clinical practice related to validity, reliability, and practicality concerns (Berger, et al., 2018). Therefore, the ASA’s *Perioperative Brain Health Initiative* advocates for the identification and evaluation of novel screening tools for predicting, identifying, and tracking POD in older surgical patients (American Society of Anesthesiologists, 2019).
The ideal cognitive screening tool for the preanesthetic assessment of baseline cognitive function would be rapid, easily-administrable, valid, reliable, automatically scored, void of language, cultural, and education bias and cost-efficient (Axley & Schenning, 2015). No such tool has been identified to date. This study systematically evaluated the utility of a novel POC EEG hardware and software system, WAVi Medical™, for perioperative neurocognitive assessment.

The WAVi Medical™ system employs auditory event-related response tests as a metric of cognition. Leveda et al. (2016) reported that P300 AEPs can be used as a neurobiomarker for even mild neurocognitive disorders. Culley et al. (2017) reported that baseline cognitive function is a strong, independent predictor for POD in older surgical patients. The WAVi Medical™ system may offer anesthesia providers a rapid and reliable neurocognitive assessment tool that could potentially be used to predict, identify, and track the progression of perioperative neurocognitive disorders (e.g., POD) in older surgical patients.

Delimitations

The data analyzed in this study was sourced from another ongoing research project that began data collection in 2020 and plans to continue through a date yet to be determined related to unanticipated, unpredictable, and prolonged research restrictions due to COVID-19. The study included only data collected within a single health system, VCU/VCUHS. VCU is an urban research university that is ranked 32nd in the nation by the NIH for its strength in interdisciplinary neuroscience research (Virginia Commonwealth University, 2019). VCUHS is a level one trauma and regional referral center that performs ~25,000 surgical procedures each year (Virginia Commonwealth University, 2019). Those evaluated in the study consisted of older
surgical patients undergoing anesthesia for elective, non-cardiac procedures lasting longer than one hour who met eligibility criteria.

Assumptions

The principal assumption in this study is that the WAVi Medical™ system provides valid and reliable assessment of P300 waveforms. This assumption was reasonable given: 1) a multitude of previous studies utilize P300 evoked potentials as a neurocognitive assessment metric, 2) at least two research teams have recently published data captured using the WAVi Medical™ system, and 3) similar ongoing neurocognitive clinical studies are employing the WAVi Medical™ system. Mulkey et al. (2019) accepted similar assumptions as the first investigators to evaluate the Ceribell device (Ceribell, Inc., 2018) as a delirium identification and assessment tool in the intensive care unit (ICU).

Definition of Terms

- **Cognition**: conscious intellectual activity (e.g., thinking, reasoning, remembering)
- **Neurocognitive**: relating to the central nervous system’s structures and processes that enable cognitive functions
- **Delirium**: a serious, abrupt change in brain function causing confusion and altered environmental awareness
- **Postoperative delirium (POD)**: the first acute event of neurocognitive impairment occurring up to one week postoperatively or discharge, whichever is first (Evered et al., 2018)
- **Predisposing risk factors**: factors that make someone inclined to a condition
- **Precipitating risk factors**: factors that cause a condition
- **Metabolic derangement:** a condition caused by an abnormal metabolic process (e.g., diabetes, obesity, hypertension)
- **Delayed neurocognitive recovery:** cognitive decline with symptoms diagnosed up to one month following surgery and anesthesia (Evered et al., 2018)
- **Postoperative neurocognitive disorder:** cognitive decline with symptoms diagnosed between one month and one year post-surgery and anesthesia (Evered et al., 2018)
- **Electroencephalography:** the measurement of electrical activity in different parts of the brain and the recording of such activity as a visual trace
- **Point-of-care testing:** testing at the place and time patient care is being provided
- **Auditory evoked potential:** a time-locked electrical signal elicited from the brain in response to an auditory stimulus
- **Event-related potential:** minute changes in the electrical activity of the brain produced by a specific event or stimulus
- **Amplitude:** the maximum distance from equilibrium of a waveform at a given point in time
- **Latency:** the delay between signal initiation and conduction
- **Vascular event:** abnormal medical condition caused by a critical vascular disease related event blocking the delivery of oxygen to body tissues (e.g., stroke or myocardial infarction)
- **Preoperative:** denoting the period before surgery
- **Intraoperative:** denoting the period during surgery
- **Postoperative:** denoting the period following surgery
- **Perioperative:** denoting the period before, during, and following surgery
- *Anesthetic depth*: the degree an anesthetic medication depresses the central nervous system

**Organization of Remaining Chapters**

The remainder of this study is organized into five chapters, a bibliography, and appendices. Chapter 2 presents a comprehensive synthesis of the literature. Chapter 3 describes the study’s guiding theory. Chapter 4 explains the study design and research methodology. The WAVi Medical™ system, the data source’s study protocol, and sample determination are delineated. Data analysis and discussion of study findings are offered in chapter 5 following the study. Chapter 6 provides a summary of key points, conclusions, and recommendations. Bibliography and appendices follow.
Chapter 2: Literature Review

Chapter Overview

Chapter two reviews literature related to perioperative neurocognitive disorders, specifically risk factors, perioperative cognitive assessment, and associated postoperative sequelae. The chapter provides a historical background for this study, defines postoperative delirium (POD), and reviews the current state of the science of perioperative brain health. A gap in the literature is established, and aims and hypotheses are presented.

Anesthetics and The Brain

Anesthetics are believed to exert their effects by altering the brain’s ability to make neuronal connections (i.e., communicate from one brain cell to another) (Flood & Shafer, 2015a). Neuronal connections are the physical basis for consciousness (Pepperell, 2018). Brain cells communicate with one another by sending neurotransmitters (i.e., chemical messenger molecules) across the gaps that exist between cells (Flood & Shafer, 2015b). These gaps are called as synapses or junctions. When one brain cell sends a signal to another brain cell, neurotransmitters (e.g., acetylcholine, dopamine, norepinephrine, gamma aminobutyric acid (GABA), glutamate, glycine, galanin, etc.) are released in response to an action potential (Flood & Shafer, 2015b). An action potential is a change in the cell’s electrical potential caused by the movement of ions (e.g., sodium, potassium, calcium, chloride, etc.) (Flood & Shafer, 2015b). Anesthesia providers administer medications that alter one or more of these neuronal communication processes (Purdon et al., 2015). Following anesthesia, these neuronal connections may not return to patients’ baseline levels in older adults as rapidly or completely as
they do in younger adults (Berger et al., 2018; Mahanna-Gabrielli et al., 2019; Wu et al., 2019; Wu et al., 2019).

Anesthesia is necessary when a patient requires surgery. However, exposing the aged brain to an anesthetic (e.g., intravenous, inhaled, or regional) may contribute to transient and/or long-lasting neurocognitive impairment (Berger et al., 2018; Mahanna-Gabrielli et al., 2019; Wu et al., 2019; Wu et al., 2019). For this reason, perioperative neurocognitive disorders are a major brain health related concern for older surgical patients (American Society of Anesthesiologists, 2019; Berger et al., 2018; Mahanna-Gabrielli et al., 2019).

**Historical Background**

On October 16, 1846 William Thomas Green Morton publicly demonstrated the use of inhaled ether as an effective anesthetic in the Bulfinch Building, now known as the Ether Dome, at Massachusetts General Hospital in Boston, Massachusetts (Fenster, 2002). Morton administered ether to Edward Abbott for the surgical removal of a mass on Abbott’s neck (Fenster, 2002). Abbott calmly awoke from surgery and his surgeon, Dr. John Collins Warren, then Dean of Harvard Medical School, famously remarked “*Gentleman, this is no humbug*” (Fenster, 2002). Since that famous day, the pain and suffering associated with surgery have been attenuated like never before. Anesthetics remarkably and reversibly reduce a patient’s state of consciousness to facilitate surgery. However, whether or not the brain returns to a state identical to its presurgical, preanesthetic state in vulnerable patients (e.g. older patients) following surgery and anesthesia has been questioned for over 130 years and increasingly critically examined for the past decade (Savage, 1887; Berger et al., 2018; Mahanna-Gabrielli et al., 2019).

Savage, a psychiatrist, was one of the first physicians to describe an altered brain state in patients following surgery and anesthesia in his presentation at the Annual Meeting of the British
Medical Association in Dublin, Ireland in 1887. At this meeting he made the case that postoperative neurocognitive disorders may not be a humbug either. Interestingly, Savage (1887) opened his presentation by stating:

> All writers and observers have noticed that it is very rarely that one cause alone is efficient for the production of any attack of insanity, and that *usually there are several predisposing causes which may have been in operation for a long time* [emphasis added], as well as one or more exciting causes which may have been in action for much shorter periods...[t]he most common form of mental disorder which comes in such cases is of the type of acute delirious mania...though such mental disorder is generally of a temporary character, it may pass into chronic weak-mindedness, or it may pass into (c) progressive dementia which cannot be distinguished from general paralysis of the insane...*any cause producing delirium may produce a more permanent disorder of the mind* [emphasis added]. (p. 1405)

One notable case presented by Savage (1887) was of an “elderly” (age not specified) clergyman who presented for surgery for rectal cancer. Following an uneventful ether anesthetic and operation, the patient’s surgeon, Mr. Croft, noted:

> [W]hen the patient became conscious, it was at once noticed that his mind was affected...[h]e was restless, incoherent, repeating meaningless expressions...[h]is memory seemed very defective...*he remained in this state for a few weeks after his return home, and then almost suddenly recovered* [emphasis added]. (p. 1406)

In another case, Savage (1887) described a young mother who experienced an altered mental state beginning several hours after the administration of a nitrous oxide-based anesthetic for dental surgery:
The patient was delirious, conjunctivae insensible, urine and feces passed involuntarily; irregular movements of all kinds were being made, and speech was incessant...[s]he never regained her senses or recognized her friends. She was in a state of delirious mania for three weeks, then settled into dementia, in which she [remained]...[t]he points of this case are the acquired nervous instability, the acute delirious mania, with its consecutive dementia [emphasis added]. (p. 1406)

Savage concluded by stating “I trust that enough evidence has been brought forward to induce others to give their experience, and thus establish a relation or destroy a fallacy [emphasis added]” (p. 1406). Sixty-eight years passed before Bedford (1955) formally and systematically did so—establish a relation.

Bedford (1955) affirmed “It is well known, too, that in elderly people transitory confusional states often follow operations under general anesthesia; but it is not so widely appreciated that minor dementias and even permeant catastrophic mental impairment may occasionally be the aftermath” (p. 6884). For this reason, Bedford systematically reviewed the medical records of “…4250 patients over the age of 65 seen in the Oxford geriatric unit at Cowley Road Hospital in the five years ending in June, 1954…1193 had undergone some operation under general anesthesia…” (p. 6884). Bedford (1955) found that thirty-four percent (410 / 1,193) of these older surgical patients had friends and family members who described that “the patient “had never been the same since operation”” (p. 6884). Bedford identified evidence to dispute this allegation in 290 / 410 patients, and then carefully evaluated the remaining 120 cases in which there were reports such as:

"He’s never been able to write a decent letter since...[anesthesia and surgery]"

"He’s become so forgetful since ..."
"She can’t be trusted to go out shopping since..."

"She’s lost all interest in the family since..."

"He’s never read a book through since..."

"He used to be so tidy but now he’s neglectful and sloppy in his habits [since]...”

"He can’t concentrate on anything since..."

"She’s become childish and unreliable since..."

"He’s not been able to attend to the business since..."

"He’s just not the same person since ...” (p. 6884)

Bedford’s (1955) report followed these anecdotal statements with 18 case-histories of patients in which Bedford personally observed a patient’s change in mental state from preoperative baseline health to extreme cases of postoperative dementia “…in which the patient became virtually a human vegetable…” following surgery and anesthesia (p. 6884). It is important to note that Bedford (1955) supported his rationale for only including the 18 cases that he personally observed in his analysis by stating:

First, the patient’s testimony may be unreliable because of his dementia…[and]

[secondly, relations and friends tend to blame any dramatic incident, such as an operation or accident, for the dementia which has in fact been slowly progressive intellectual degradation, antedating to the operation or accident…hence the incident is blamed, albeit falsely, for the dementia [emphasis added]. (p. 6884)

Another decade passed before rigorous evaluation of cognitive changes following cardiac surgery began in the 1960s (Evered et al., 2016).

An ardent academic interest in cognitive dysfunction at that time largely occurred in response to a series of reports implicating the cardiopulmonary bypass machine as a potential
causative mechanism for altered neurocognition following open-heart surgery (Blachy & Starr, 1964; Egerton & Kay, 1964; Heller et al., 1970; Kornfeld et al., 1965). Shaw et al., (1987) conducted one of the first prospective studies to evaluate perioperative cognitive function in 259 patients prior to, one week after, and six months following cardiac surgery using a battery of 10 neuropsychological tests. Following multivariate analysis of 91 potential contributory mechanisms, only “cardiac failure before surgery and global impairment of left ventricular function” correlated with long-term neurocognitive decline (Shaw et al., 1987). More recent evidence also demonstrates that cardiopulmonary bypass alone does not cause neurocognitive dysfunction following open-heart surgery (Soenarto et al., 2018). A significant number of older surgical patients present with postoperative neurocognitive alterations following an array of both cardiac and non-cardiac surgeries (Rudolph & Marcantonio, 2011). Table one lists 84 studies conducted over the last fifty years reporting the wide-ranging, but significant incidence of cognitive changes in older surgical patients following a variety of surgical procedures.

Table 1

*Reported Incidence of Cognitive Changes Following a Variety of Surgical Procedures*

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Incidence of Postoperative Cognitive Change</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>41%</td>
<td>Egerton &amp; Kay, 1964</td>
</tr>
<tr>
<td>Cardiac</td>
<td>19%</td>
<td>McClish et al., 1968</td>
</tr>
<tr>
<td>Cardiac</td>
<td>17%</td>
<td>Kimball, 1969</td>
</tr>
<tr>
<td>Cardiac</td>
<td>31%</td>
<td>Rubenstein &amp; Thomas, 1969</td>
</tr>
<tr>
<td>Cardiac</td>
<td>25%</td>
<td>Heller et al., 1970</td>
</tr>
<tr>
<td>Cardiac</td>
<td>24%</td>
<td>Morgan, 1971</td>
</tr>
<tr>
<td>Cardiac</td>
<td>74%</td>
<td>Kimball, 1972</td>
</tr>
<tr>
<td>Cardiac</td>
<td>66%</td>
<td>Frank et al., 1972</td>
</tr>
<tr>
<td>Cardiac</td>
<td>59%</td>
<td>Freyhan et al., 1971</td>
</tr>
<tr>
<td>Cardiac</td>
<td>31%</td>
<td>Kornfield et al., 1974</td>
</tr>
<tr>
<td>Cardiac</td>
<td>28%</td>
<td>Kornfield et al., 1978</td>
</tr>
<tr>
<td>Cardiac</td>
<td>23%</td>
<td>Summers, 1979</td>
</tr>
<tr>
<td>Cardiac</td>
<td>72%</td>
<td>Sadler, 1981</td>
</tr>
<tr>
<td>General</td>
<td>18%</td>
<td>Millar, 1982</td>
</tr>
<tr>
<td>Procedure</td>
<td>Mortality Rate</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Cardiac</td>
<td>68%</td>
<td>Owens &amp; Hutelmyer, 1982</td>
</tr>
<tr>
<td>Orthopedic&lt;sup&gt;b&lt;/sup&gt;</td>
<td>52%</td>
<td>Williams et al., 1985</td>
</tr>
<tr>
<td>Urologic</td>
<td>7%</td>
<td>Chung et al., 1987</td>
</tr>
<tr>
<td>Orthopedic (hip fracture)</td>
<td>43%</td>
<td>Gutstafson et al., 1988</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0%</td>
<td>Schindler et al., 1989</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>28%</td>
<td>Rogers et al., 1989</td>
</tr>
<tr>
<td>Urologic</td>
<td>5%</td>
<td>Chung et al., 1989</td>
</tr>
<tr>
<td>Lung Transplant</td>
<td>73%</td>
<td>Craven et al., 1990</td>
</tr>
<tr>
<td>All</td>
<td>10%</td>
<td>Egbert et al., 1990</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>53%</td>
<td>Gufstafson et al., 1991</td>
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<tr>
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<td>48%</td>
<td>Gufstafson et al., 1991</td>
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<td>41%</td>
<td>Williams-Russo et al., 1992</td>
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<td>Vascular</td>
<td>10%</td>
<td>Marcantonio et al., 1994</td>
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<tr>
<td>Orthopedic</td>
<td>9%</td>
<td>Marcantonio et al., 1994</td>
</tr>
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<td>Cardiac (aortic aneurysm)</td>
<td>41%</td>
<td>Marcantonio et al., 1994</td>
</tr>
<tr>
<td>Thoracic (noncardiac)</td>
<td>14%</td>
<td>Marcantonio et al., 1994</td>
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<tr>
<td>Abdominal</td>
<td>5%</td>
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</tr>
<tr>
<td>Orthopedic</td>
<td>9%</td>
<td>Marcantonio et al., 1994</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>18%</td>
<td>Fischer &amp; Flowerdew, 1995</td>
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<tr>
<td>Orthopedic (hip fracture)</td>
<td>47%</td>
<td>Bowman, 1997</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>27%</td>
<td>Bowman, 1997</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>17%</td>
<td>Kaneko et al., 1997</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>10%</td>
<td>Litaker et al., 1998</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>11%</td>
<td>Lynch et al., 1998</td>
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<td>11%</td>
<td>Edlund et al., 1999</td>
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<td>5%</td>
<td>Silverstein et al., 1999</td>
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<td>Orthopedic (hip fracture)</td>
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<td>Brauer et al., 2000</td>
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<td>24%</td>
<td>Duppils et al., 2000</td>
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<td>12%</td>
<td>Duppils &amp; Wikblad, 2000</td>
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<td>Andersson et al., 2001</td>
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<tr>
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<td>5%</td>
<td>Andersson et al., 2001</td>
</tr>
<tr>
<td>Orthopedic (hip fracture)</td>
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<td>Galanakis et al., 2001</td>
</tr>
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<td>27%</td>
<td>Edlund et al., 2001</td>
</tr>
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<td>Galanakis et al., 2001</td>
</tr>
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<td>Reference</td>
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<td>---------------------------</td>
<td>---------</td>
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<td>Vascular</td>
<td>36%</td>
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<td>Cataract</td>
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<td>Milstein et al., 2002</td>
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<td>Orthopedic (hip fracture)</td>
<td>4%</td>
<td>Johansson et al., 2002</td>
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<td>Thakur et al., 2002</td>
</tr>
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<td>Orthopedic</td>
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<td>Zakriya et al., 2002</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>10%</td>
<td>Linstedt et al., 2002</td>
</tr>
<tr>
<td>Vascular</td>
<td>39%</td>
<td>Böhner et al., 2003</td>
</tr>
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<td>Orthopedic (hip fracture)</td>
<td>14%</td>
<td>Morrison et al., 2003</td>
</tr>
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<td>Orthopedic (hip fracture)</td>
<td>20%</td>
<td>Schuurmans et al., 2003</td>
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<td>Forminga et al., 2003</td>
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<td>Vascular</td>
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<td>Kantznelson et al., 2009</td>
</tr>
<tr>
<td>Abdominal</td>
<td>25%</td>
<td>Morimoto et al., 2009</td>
</tr>
<tr>
<td>Spine</td>
<td>14%</td>
<td>Lee &amp; Park, 2009</td>
</tr>
<tr>
<td>Spine</td>
<td>7-28%</td>
<td>Ushida et al., 2009</td>
</tr>
<tr>
<td>Vascular</td>
<td>23%</td>
<td>Koebrugge et al., 2010</td>
</tr>
<tr>
<td>Vascular</td>
<td>29%</td>
<td>Sasajima et al., 2012</td>
</tr>
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<td>Vascular</td>
<td>25%</td>
<td>Kawatani et al., 2015</td>
</tr>
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<td>Vascular</td>
<td>5%</td>
<td>Visser et al., 2015</td>
</tr>
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<td>Vascular</td>
<td>15%</td>
<td>Raats et al., 2015</td>
</tr>
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<td>Vascular</td>
<td>17%</td>
<td>Raats et al., 2015</td>
</tr>
<tr>
<td>Vascular</td>
<td>12%</td>
<td>Sugimoto et al., 2015</td>
</tr>
<tr>
<td>All</td>
<td>2%</td>
<td>Lin et al., 2016</td>
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<td>Orthopedic (hip fracture)</td>
<td>71%</td>
<td>Watne et al., 2016</td>
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<td>Spine</td>
<td>8%</td>
<td>Soh et al., 2017</td>
</tr>
<tr>
<td>Cardiac</td>
<td>24%</td>
<td>Lei et al., 2017</td>
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</table>
Table 1 Continued

<table>
<thead>
<tr>
<th></th>
<th>Incidence (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine</td>
<td>18%</td>
<td>Kang et al., 2020</td>
</tr>
<tr>
<td>Non-cardiac</td>
<td>12%</td>
<td>Iamaroon et al., 2020</td>
</tr>
</tbody>
</table>

Note: Studies are listed in chronological order.

a: Reported incidence (%) of postoperative cognitive change is rounded to nearest whole number

b: Orthopedic refers to elective procedures (e.g., hip or knee arthroplasty) unless otherwise specified

Postoperative cognitive changes in older surgical patients have been reported following general anesthesia, sedation, and spinal anesthesia (Evered et al., 2011; Ilango et al., 2016; Patel et al., 2018). Miller et al. (2018) conducted a systematic review of 28 randomized controlled trials (RCTs) totaling 4,507 patients across a variety of surgical procedures and concluded that current best evidence is also inconclusive as to whether or not the incidence of POD varies between patients receiving general anesthesia with inhalational anesthetics (e.g., isoflurane, sevoflurane, desflurane) versus intravenous anesthetics (e.g., propofol), but reported “with low-certainty” that postoperative cognitive dysfunction may be reduced when patients receive a propofol-based total intravenous anesthetic (p. 2).

Ehsani et al. (2020) recently reported a lower incidence of postoperative cognitive dysfunction and delirium following spinal anesthesia (4.25%) versus general anesthesia (29.7%) in a small cohort of 94 patients over the age of 50 years presenting for hip fracture fixation indicating that further inquiry is still needed related to assessment techniques and potential contributory mechanisms. One thing is for certain, a growing body of research continues to investigate whether or not the brain returns to an identical preanesthetic state in vulnerable patients (e.g., patients age 60 years and older) following surgery and anesthesia (Berger et al., 2018; Mahanna-Gabrielli et al., 2019; Wu et al., 2019).
Heterogeneity of Prior Studies

As one can observe from Table one, the reported incidence of neurocognitive changes following surgery in a single patient population (e.g., orthopedic hip fracture repair) varies significantly (5-71%). Reported explanations for this strikingly wide range center around the significant heterogeneity of these studies (Bruce et al, 2007; Evered et al., 2018; Rudolph & Marcantonio, 2011). Sample populations, assessment tools, and assessment epochs varied greatly among the studies (Bruce et al, 2007; Evered et al., 2018; Rudolph & Marcantonio, 2011).

As an example, in the 17 studies evaluating neurocognitive changes following hip fracture repair listed in Table one, six different assessment tools were used including: Neecham Confusion Scale (1 study), CAM (8 studies), Diagnostic and Statistical Manual of Mental Disorders (DSM) editions 3 and 4 (7 studies), Organic Brain Disorders assessment (4 studies), and the Delirium Rating Scale (1 study). Eleven of these studies employed a single assessment scale, and six incorporated two assessment scales. Sample sizes ranged from 10 to 546 study participants. The mean age of study participants, when reported, ranged from 65-92. Varied assessment epochs across these studies included: daily, twice daily, postoperative days 1 or 2 and at discharge, postoperative day 5 only, and postoperative day 7 only. Similarly, in patients presenting for cardiac surgery “…the incidence of delirium using chart review was 3%, noted during routine clinical care was 8%, using interviews with nurses was 9%, and using daily mental status testing and application of a validated diagnostic algorithm was 53%” (Evered et al., 2018, p. 874).

Another major barrier to comparing data from prior postoperative cognition studies is the varied operationalization of study terms (e.g., confusion, delirium, postoperative cognitive dysfunction) (Evered et al., 2018). For this reason, recommendations for standardized
nomenclature of cognitive changes following surgery and anesthesia were proposed by Evered and colleagues in 2018 (Evered et al., 2018). These recommendations were developed using “a modified Delphi procedure with no prespecified number of rounds comprised of three face-to-face meetings followed by online editing of draft versions” by a multispecialty working group (Evered et al., 2018, p.872). The recommendations propose a shift away from a previously used umbrella term, postoperative cognitive dysfunction, to a well-defined time and score-grouped classification system of perioperative neurocognitive disorders (Evered et al., 2018; Mahanna-Gabrielli et al., 2019). Evered et al.’s (2018) recommended classification system for perioperative neurocognitive disorders categorized according to the timing of onset of the disorder is summarized by Figure 2.

**Figure 2**

*Standardized Nomenclature of Perioperative Neurocognitive Disorders*

<table>
<thead>
<tr>
<th>Umbrella Term</th>
<th>Recommended Terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative Cognitive Dysfunction (POCD)</td>
<td><em>Baseline neurocognitive disorder – mild/major</em></td>
</tr>
<tr>
<td></td>
<td><em>Surgery &amp; Anesthesia</em></td>
</tr>
<tr>
<td></td>
<td><em>Postoperative delirium (POD)</em></td>
</tr>
<tr>
<td></td>
<td><em>Up to Postoperative Day 7</em></td>
</tr>
<tr>
<td></td>
<td><em>Delayed neurocognitive recovery (dNCNR)</em></td>
</tr>
<tr>
<td></td>
<td><em>Up to 30 days after surgery &amp; anesthesia</em></td>
</tr>
<tr>
<td></td>
<td><em>Postoperative neurocognitive disorder – mild/major</em></td>
</tr>
<tr>
<td></td>
<td><em>&gt; 30 days after surgery &amp; anesthesia</em></td>
</tr>
</tbody>
</table>

Note: Image adapted from Mahanna-Gabrielli et al. (2019).
This study incorporated neurocognitive assessments that were performed at patients’ baseline and postoperative day one to explore baseline and postoperative neurocognitive characteristics that may help to establish novel predictive and trend metrics for perioperative neurocognitive assessment in older surgical patients.

**Postoperative Delirium (POD)**

The clinical diagnosis of delirium was first standardized by the American Psychiatric Association in their Diagnostic and Statistical Manual of Mental Disorders (DSM) 3rd edition (Oosterhous et al., 2017). The DSM is an authoritative guide used by healthcare professionals worldwide to diagnosis mental disorders (American Psychiatric Association, 2021). Delirium is an acute change in global cognitive function and attention that presents with varying symptoms and results from an organic etiology (Mulkey et al., 2018). POD is a term used to describe the first acute event of neurocognitive impairment, that aligns with the DMS-5 criteria, occurring up to one week following surgery and anesthesia or prior to hospital discharge, whichever occurs first (Evered et al., 2018). Evered et al. (2018) were the first to operationalize the term POD based on DSM-5 criteria and recommend this standardized nomenclature be used in research and clinical practice. DSM-5 delirium criteria are listed in Table two (American Psychiatric Association, 2013).

POD presents as an acute onset of altered executive functions. The term executive functions refers to one’s ability to learn, think, reason, remember, problem solve, decide, and pay attention. These cognitive processes essentially define one’s ability to organize and participate in daily activities. A patient experiencing POD may be tired and sluggish (i.e. present with hypoactive delirium), restless and distressed (i.e., present with hyperactive delirium), or a combination of both for up to one week following surgery and anesthesia (American Geriatrics
Table 2

Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Delirium Criteria

| A | Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment). |
| B | The disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day. |
| C | An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception). |
| D | The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma. |
| E | There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies. |

Society, 2015). Hypoactive delirium accounts for ~50% of delirium cases, mixed hypo- and hyperactive delirium for ~30% of cases, and hyperactive delirium for only 20% of cases (Hosker & Ward, 2017).

Over 50% of patients who experience postoperative delirium present with signs of delirium on postoperative day one (Iamaroon et al., 2020; Lin et al., 2016). However, the most common presentation of delirium, the hypoactive form, is more difficult to identify in clinical practice and for this reason often goes undiagnosed (Collins, 2010; Hosker & Ward, 2017). Figure 3 differentiates the clinical signs and symptoms hyper- versus hypoactive delirium.

POD is believed to present with varied and fluctuating symptoms that can differ from patient to patient as the result of increased dopamine, decreased acetylcholine, and divergent amalgamations of other neurotransmitters (e.g., norepinephrine, glutamate, serotonin, and GABA) among patients (Numan et al., 2017 as cited by Mulkey et al., 2019).
Incidence

According to the American Geriatrics Society (2015), 19 million older adults in the United States (US) present for surgery and anesthesia each year, and 4.5-9 million (~25-50%) of these patients experience POD following surgery. The highest reported incidence of POD in a prospective sample of older surgical patients is 71% (Watne et al., 2016). However, the reported incidence varies greatly (2-71%) throughout the literature largely related to the significant heterogeneity among studies as previously discussed. Table one lists examples. The challenge in clinically identifying the hypoactive form of delirium may also have led to the relatively low reported incidence of POD in some studies (Hosker & Ward, 2017; Olotu, 2019). Collins et al. (2010) reported that 72% of patients who met criteria for a clinical diagnosis of delirium were unidentified when presenting with hypoactive signs. Regardless, POD is the most prevalent complication associated with surgery and anesthesia among older adult patients (American Geriatrics Society, 2015; American Society of Anesthesiologists, 2019).
Of additional concern is that a subset of patients who experience POD, 12-21%, following non-cardiac surgery develop a postoperative neurocognitive disorder lasting up to 3 months, and 10% exhibit reduced cognitive function one to two years later (Abildstrom et al., 2000; Evered & Silbert, 2018). POD is problematic because the condition distresses patients, their loved ones, and care providers; it is also associated with inferior functional recovery, and increased healthcare spending (Hernandez et al., 2017; Hshieh et al., 2017; Inouye et al., 2014; Zywiel et al., 2015).

Sequelae Associated with Postoperative Delirium (POD)

Patients experiencing POD present with varying degrees of consciousness (e.g., hyper- or hypoactive) and demonstrate a combination of intellectual, attention, and memory-related impairments (Inouye et al., 2014; Munk et al., 2016). This state of disorganized thinking and inattention not only distresses patients, family members and caregivers, but is also associated with increased length of hospitalization, patient morbidity and mortality, and progression to delayed or incomplete neurocognitive recovery (Jin et al., 2020; Koster et al., 2012; Saczynski et al., 2012). Based on a prospective observational study of 566 older patients presenting for elective surgery, Hshieh et al. (2017) concluded that POD was associated with “clinically meaningful impairment of functional recovery” for up to 18 months postoperatively (p. 647). Koster et al. (2012) reported that delirium following elective cardiac surgery is associated with a seven-fold increased mortality risk, a nearly two-fold increase in the likelihood of hospital readmission, and a reduction in patients’ quality of life in a sample of 300 patients.

POD is also associated with delayed neurocognitive recovery and may be predictive of postoperative neurocognitive disorders (Sprung et al., 2017). Bickel et al. (2008) followed 41 patients who experienced POD following hip surgery and reported that 53.8% of these patients
experienced cognitive impairment 38 months after surgery. Additionally, “[l]ogistic regression analysis adjusted for age, sex, medical comorbidity and preoperative cognitive performance revealed highly significant associations between delirium and cognitive impairment (OR = 41.2; 95% CI = 4.3-396.2), subjective memory decline (OR = 6.2; 95% CI = 1.5-25.8), and incident need for long-term care (OR = 5.6; 95% CI = 1.6-19.7)” (Bickel et al., 2008, p. 26). Patients who experience POD are also more likely to be diagnosed with dementia or experience long-term cognitive decline than patients who have not experienced POD (Aranake-Chrisinger & Avidan, 2017; Saczynski et al., 2012; Sprung et al., 2017; Vasunilashorn et al., 2018). Whether POD contributes to or is evidence of impending dementia is unclear.

Leslie et al. (2008) reported that patient care costs more than double in hospitalized patients with delirium (Leslie et al., 2008). Inouye et al. (2014) reported that annual delirium costs exceed $164 billion in the US and $182 billion in Europe. Zyweil et al. (2015) reviewed a surgical database from a single urban academic medical center to investigate the impact of POD on health care costs in 242 older patients after hip fracture surgery. POD was associated with an average cost increase of $8,286 dollars per patient, and the total increased cost associated with POD over the course of the two-year study was $961,131 dollars (Zyweil et al., 2015). Table three lists postoperative sequelae associated with POD.

**Risk Factors**

Over 30 predisposing and precipitating risk factors for POD have been reported. They are summarized in Table four (Mahanna-Gabrielli et al., 2019). Several risk assessment and POD-prediction tools have recently been proposed for use during the preoperative anesthetic assessment in an effort to risk-stratify older surgical patients and efficiently allocate limited healthcare resources (Jin et al., 2020). However, the value of these screening tools is yet to be
Table 3

*Postoperative Sequelae Associated with Postoperative Delirium (POD)*

<table>
<thead>
<tr>
<th>Postoperative Sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Distress for patients, loved ones, and caregivers (Koster et al., 2012)</td>
</tr>
<tr>
<td>- Diminished functional recovery (Koster et al., 2012)</td>
</tr>
<tr>
<td>- Prolonged length of stay (Raats et al., 2015)</td>
</tr>
<tr>
<td>- Increased care dependency (Hshieh et al., 2017)</td>
</tr>
<tr>
<td>- Increased long-term morbidity risk (Gleason et al., 2016)</td>
</tr>
<tr>
<td>- Risk of long-term cognitive decline (Aranake-Chrisinger &amp; Avidan, 2017)</td>
</tr>
<tr>
<td>- Increased mortality risk (Maniar et al., 2016; Raats et al., 2015)</td>
</tr>
<tr>
<td>- Increased healthcare costs (Brown et al., 2016, Maniar et al., 2016)</td>
</tr>
</tbody>
</table>

Table 4

*Risk Factors for the Development of Postoperative Delirium (POD)*

<table>
<thead>
<tr>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Pre-existing cognitive impairment</td>
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<tr>
<td>Impaired vision or hearing</td>
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<tr>
<td>Severe illness</td>
</tr>
<tr>
<td>Preoperative infection</td>
</tr>
<tr>
<td>Poor functional status</td>
</tr>
<tr>
<td>Metabolic derangements</td>
</tr>
<tr>
<td>Polypharmacy</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
</tr>
</tbody>
</table>

determined because they have either been developed in medical, rather than surgical, patient populations (e.g., Iounye et al., 1993) or yet to be validated outside of a single surgical procedure (e.g., Kalisvaart et al., 2006 and Kim et al., 2020). One tool, the Delirium Prediction Based on Hospital Information (DELPHI), was validated in a small sample of 553 patients undergoing trauma, vascular, or abdominal surgery at a single medical center (Kim et al., 2016). Risk factors incorporated into the DELPHI model were: age, low physical activity, hearing impairment, heavy alcoholism, history of prior delirium, ICU admission, emergency surgery, open surgery, and increased preoperative C-reactive protein (Kim et al., 2016). However, the DELPHI’s
predictive value in this small single-center study was only 70%, and the tool has yet to be externally validated (Jin et al., 2020).

Mitigation Strategies

Delirium is reportedly preventable in up to 40% of patients (Siddiqi et al., 2016). In an effort to prevent delirium, the American Geriatrics Society (2015) recommends that anesthesia providers “avoid medications that induce delirium postoperatively in older adults (p. 140).” According to the American Geriatrics Society (2015), these medications include: drugs with anticholinergic properties (e.g., famotidine—a commonly used perioperative histamine (H2-receptor) antagonist), corticosteroids (e.g., dexamethasone—a commonly used antiemetic and anti-inflammatory), meperidine, sedative hypnotics (e.g., midazolam—a commonly used preoperative sedative and anxiolytic), and polypharmacy (i.e. combining five or more medications—which is a common practice as part of enhanced recovery after surgery (ERAS) protocols). Unfortunately, all medications commonly utilized to produce general anesthesia (e.g., propofol, sevoflurane, desflurane, and isoflurane) have been associated with the development of POD in older surgical patients (Kinjo et al., 2019; Sieber et al., 2018). Additionally, Patel et al. (2018) reported that, based on the limited evidence available, regional anesthesia (i.e., the injection of local anesthetics in proximity to a target nerve to block pain impulses from a region of the body) versus general anesthesia does not reduce the incidence of POD in older patients following hip fracture surgery.

Providers, however, cannot omit every anesthetic agent and technique when an older patient requires surgery. Rather than omitting anesthetics agents, emerging research is considering the possibility that co-administering potentially neuroprotective anesthetic adjunct medications may preserve or perhaps even enhance patients’ neurocognitive function. Messick et
al. (1987) defined neuroprotection as the “prevention or amelioration of neuronal damage evidenced by abnormalities in cerebral metabolism, histopathology or neurologic function occurring after a hypoxic or an ischemic event” (as cited in Hudetz et al., 2010, p. 131). Hudetz et al. (2010) described the two goals of neuroprotection: 1) prevent cerebral ischemia and 2) promote the recovery of ischemic neuronal tissue. Examples of potentially neuroprotective anesthetic adjunct medications reported in the literature include ketamine, magnesium, and lidocaine.

Rascón-Martínez et al. (2016) evaluated the impact of intraoperative ketamine on postoperative neurocognitive function in a sample of 65 older patients undergoing ophthalmic surgery. The investigators evaluated participants’ cognitive function pre- and post-operatively using the Short Portable Mental Status Questionnaire (SPMSQ) (Rascón-Martínez et al., 2016). Participants either received 0.3mg/kg ketamine intraoperatively or placebo (Rascón-Martínez et al., 2016). Baseline preoperative SPMSQ scores were similar for both study groups (Rascón-Martínez et al., 2016). However, participants who received intraoperative ketamine demonstrated improved SPMSQ scores relative to their baseline (Rascón-Martínez et al., 2016). The postoperative SPMSQ scores of participants who received the placebo were essentially unchanged from baseline (Rascón-Martínez et al., 2016). A systematic review and meta-analysis by Hovaguimian et al. (2018) concluded that ketamine seemed to lower the risk of postoperative cognitive dysfunction [RR 0.34, 95% CI [0.15, 0.73]], but not the risk for POD [RR 0.83, 95% CI [0.25, 2.80]]. However, the quality of available evidence for this review was deemed to be low to very-low (Hovaguimian et al., 2018). The authors advocated that future research is needed to “further clarify the efficacy of ketamine on neurocognitive outcomes” (p. 1182).
Bilotta et al. (2013) conducted a qualitative review of RCTs to identify potentially neuroprotective perioperative pharmacological strategies. The authors identified two trials demonstrating that intraoperative lidocaine infusions were neuroprotective, and two trials concluding that intraoperative lidocaine infusions failed to offer neuroprotection (Bilotta et al., 2013). The two trials that did not demonstrate a neuroprotective effect may have failed to do so as a result of “…too short of an infusion period, an excessively high dose, or having included diabetic patients who might be at an increased risk of neurological injury or a different sensitivity to lidocaine” (Bilotta et al., 2013, p. 115). A more recent RCT comparing intraoperative lidocaine infusions to normal saline placebo reported that lidocaine infusions attenuated postoperative cognitive impairment in older patients following spine surgery (Chen et al., 2015). Similar to ketamine, further research is needed to elucidate the potential perioperative neuroprotective effects of lidocaine infusions.

Magnesium is also identified in the literature as a potentially neuroprotective anesthetic adjunct medication. Bhudia et al. (2007) enrolled 350 participants in an RCT comparing postoperative neurocognition between participants who received magnesium versus placebo during cardiac surgery. The authors identified that the magnesium group demonstrated better short-term postoperative cognitive function, notably in short-term memory, than the placebo group (Bhudia et al., 2007). Mack et al. (2009) conducted a double-blind placebo-controlled trial to evaluate the neuroprotective potential of intraoperative magnesium administration in 108 older surgical patients (mean age of 68 years) undergoing carotid endarterectomy. The authors reported that participants in the magnesium group demonstrated less postoperative cognitive decline than those receiving placebo [OR 0.09, 95% CI 0.02-0.5, p<0.01] (Mack et al., 2009).
While available evidence is limited in both number and quality, the potential neuroprotective effects of ketamine, lidocaine, and magnesium warrant further inquiry. Of particular interest, and yet to be evaluated in the setting of postoperative delirium in older surgical patients, is the possible synergistic effect of potentially neuroprotective anesthetic adjunct medications. Mendonca et al. (2020) reported a positive synergistic effect using a combination of lidocaine and magnesium for perioperative pain management. Fang et al. (2020) reported that combining lidocaine with ketamine “may be beneficial in shortening the onset of anesthesia, promoting postoperative awakening…and [reducing the] incidence of adverse reactions” compared to administering ketamine alone (p. 1). These findings were based on a case-control study of 586 pediatric patients (Fang et al., 2020). It is possible that similar synergistic effects exist related to neuroprotection in older surgical patients.

Potential benefits of varied pharmacological treatment strategies are challenging to ascertain when 1) the etiology of POD is not fully understood and 2) clinically utilized questionnaire-based neurocognitive assessment tools (e.g., MoCA, Mini-Cog©, and CAM)) provide a simple estimate of gross neurocognitive function, and 3) the accuracy and utility of questionnaire-based neurocognitive assessments are questionable in certain subpopulations, such as African American patients as well as patients with low socioeconomic and education levels. This study evaluated for mean group differences in potential EEG-based postoperative neurocognitive biomarkers (i.e., P300 amplitude and latency) between participants who received two or more potentially neuroprotective anesthetic adjunct medications and those who did not.

Pathophysiology

The pathophysiology of delirium is not fully elucidated. Available evidence is largely derived from animal models as human studies are limited (Jin et al., 2020). Prominent etiological
hypotheses include: 1) the neurotransmitter hypothesis, 2) the stress response hypothesis, 3) the neuroinflammation hypothesis, 4) the Alzheimer acceleration hypothesis, and 5) the cerebral vascular hypothesis, 6) metabolic derangements, 7) electrolyte imbalances, 8) and genetic factors (Inouye et al., 2014; Mahanna-Gabrielli et al., 2019; Jin et al., 2020). These hypotheses more likely complement rather than compete with one another as the etiology of delirium is likely multifactorial (Inouye et al., 2014; Mahanna-Gabrielli et al., 2019; Jin et al., 2020). Table five summarizes these hypotheses.

**Table 5**

**A Summary of Etiological Hypotheses for Delirium**

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Brief Description</th>
</tr>
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<tbody>
<tr>
<td>1. Neurotransmitter Hypothesis</td>
<td>Altered levels of circulating neurotransmitters (e.g., acetylcholine and dopamine) contribute to delirium.</td>
</tr>
<tr>
<td>2. Stress Response Hypothesis</td>
<td>Perioperative stress impairs the hypothalamic-pituitary-adrenal axis, stimulates the release of cortisol, and alters physiologic concentrations of both inflammatory mediators (e.g., cytokines) and neurotransmitters that contribute to delirium.</td>
</tr>
<tr>
<td>3. Neuroinflammation Hypothesis</td>
<td>The neuroinflammatory response associated with surgery and anesthesia triggers the release of pro-inflammatory mediators (e.g., interleukins, prostaglandins, C-reactive protein, and tumor necrosis factor) that may interrupt the blood-brain barrier’s integrity and contribute to delirium.</td>
</tr>
<tr>
<td>4. Alzheimer’s Acceleration Hypothesis</td>
<td>Surgical patients may present for surgery and anesthesia with previously undiagnosed or subclinical Alzheimer’s disease that is identified postoperatively.</td>
</tr>
<tr>
<td>5. Cerebral Vascular Hypothesis</td>
<td>Preexisting subclinical cerebral vascular disease/events may predispose a subset of patients to delirium.</td>
</tr>
<tr>
<td>6. Oxygen Deprivation Hypothesis</td>
<td>A reduction in cerebral oxidative metabolism (i.e., the physiologic process by which oxygen is used to produce the energy substrate adenosine triphosphate from carbohydrates) contributes to delirium.</td>
</tr>
<tr>
<td>7. Cellular Signaling Hypothesis</td>
<td>Alterations in intraneuronal signal transduction mechanisms contribute to delirium.</td>
</tr>
</tbody>
</table>

The predominant hypothesis discussed throughout the literature is the neurotransmitter hypothesis. This is likely because several other hypotheses ultimately result in alterations in the
synthesis, storage, and/or release of neurotransmitters (Mulkey et al., 2019). Nine different neurotransmitters are purported to contribute to delirium including: acetylcholine, dopamine, GABA, melatonin, tryptophan, serotonin, glutamate, norepinephrine, and epinephrine (Inouye et al., 2014). However, the vast majority of experimental and observational evidence focuses on the role that acetylcholine and dopamine play in the pathophysiology of delirium (Inouye et al., 2014). This focus is likely related to the clinical use of anticholinergic and dopaminergic medications in the perioperative and intensive care settings where delirium is often identified (Inouye et al., 2014).

Acetylcholine, a combination of acetic acid and choline, is a neurochemical messenger responsible for a wide variety of cell-to-cell communications throughout the body (Sam & Bordoni, 2020). In the brain, acetylcholine promotes arousal, motivation, attention, and memory (Sam & Bordoni, 2020). For this reason, researchers are working to identify specific neurologic circuits through which acetylcholine carries out these functions as potential treatment targets for altered neurocognitive states (Venkatesan et al., 2020). Simply stated, a decrease in acetylcholine concentrations in the brain and central nervous system is thought to be a primary contributory mechanism of delirium (Plaschke et al., 2007). For this reason, the American Geriatrics Society (2015) recommends avoiding anticholinergic medications (e.g., scopolamine and amitriptyline), when possible, in older surgical patients.

Dopamine, the precursor to norepinephrine in the catecholamine synthesis pathway, is another neurochemical messenger involved with an array of physiologic functions. In the brain, dopamine plays a key role in facilitating cognition and behavior. Dopamine levels can impact mood, attention, memory, learning, motor function, and hormone release. Increased levels of
dopamine in the brain are thought to play a major contributory role in states of hyperactive delirium (i.e., agitation, combativeness, and hallucinations / delusions) (Mulkey et al., 2018).

Electroencephalography

Electroencephalography (EEG) changes, specifically frequency-band power ratios (e.g., theta/alpha ratio), associated with altered neurotransmitter concentrations are reportedly some of the most dependable delirium biomarkers (Maldonado, 2008). EEG is also useful in differentiating delirium caused by an organic etiology versus a functional or psychiatric disorder (Inouye et al., 2014). Provider administered questionnaire-based neurocognitive assessments (e.g., MoCA, Mini-Cog©, and CAM) do not differentiate this level of detail related to the causal etiology of altered neurocognitive states. EEG-based assessment of cognitive function and the ability to differentiate patients according to their baseline neurocognitive state may aid to identify and stratify older surgical patients based on their risk for developing POD, inform anesthesia care plans, and develop perioperative brain health protocols to mitigate postoperative neurocognitive disorders.

In 1890, Adolf Beck reported the use of electrodes to note changes in the brain’s electrical activity in response to a stimulus (Coenen & Zayachkivska, 2013). In 1924, Hans Berger captured and graphed these changes to produce an EEG (Gibbs, F., A., Gibbs, & Lennox, 1937). In 1937, Gibbs et al. reported that anesthetic medications caused predictable and consistent changes in the amplitude and frequency of the EEG waveform. As the science evolved and demonstrated correlation between EEG changes and a patient’s state of consciousness, the concept of EEG-guided anesthesia emerged (Martin, Faulconer, & Bickford, 1959). However, EEG-guided anesthesia has not become routine because few anesthesia providers are trained in the complex skill of raw EEG analysis and interpretation (Purdon et al., 2015).
As technology advances and becomes more user-friendly, new POC EEG assessment modalities may offer clinicians the ability to rapidly perform and interpret EEG-based neurocognitive assessments. The ability to do so could be important in advancing the state of the science of POD since some have argued, hypothetically, that postoperative neurocognitive decline is a *post hoc, ergo propter hoc* (i.e., after this, therefore because of this) misattribution fallacy (Avidan & Evers, 2016). That is to say that some researchers believe that postoperative neurocognitive decline is the identification of preexisting, undiagnosed decline in a patient’s neurocognitive trajectory (Avidan & Evers, 2016). Figure 4 illustrates Avidan and Evers’ (2016) hypothetical perioperative neurocognitive trajectory model.

**Figure 4**

*Hypothetical Perioperative Cognitive Trajectory*

Preexisting, undiagnosed or subclinical cognitive impairment has been identified in a significant number of surgical patients when a battery of neuropsychological tests are employed.
Evered et al. (2011) identified that 20% of 152 patients over the age of 60 years presenting for hip replacement surgery demonstrated significant preexisting cognitive impairment defined as a score two standard deviations below the norm on at least two of seven neuropsychological assessments. Silbert et al. (2015) conducted a prospective observational trial of 300 patients presenting for hip replacement surgery and 51 nonsurgical patients age 60 years or greater and identified preexisting cognitive impairment in 32% of patients when assessed using a battery of eight neuropsychological assessments including the: Consortium to Establish a Registry in Alzheimer Disease (CERAD) test, Auditory Verbal Learning Test, Trail Making Test Parts A and B, Digit Symbol Substitution Test, Controlled Oral Word Association Test, CERAD Semantic Fluency Test, and Grooved Pegboard Test. Scott et al. (2018) reported that 51.7% of 437 patients presented for left heart catheterization with preexisting neurocognitive impairment using a battery of both written and computerized assessments including the: CERAD Auditory Verbal Learning Test, Trail Making Test Parts A and B, Digit Symbol Substitution Test, Controlled Oral Word Association Test, CERAD Semantic Fluency test, and Grooved Pegboard test.

Assessing EEG biomarkers alone or in combination with questionnaire-based cognitive assessments may improve both the clinical detection of preexisting cognitive impairment as well as the prediction and detection of postoperative neurocognitive alterations (Mulkey et al., 2018). Tanabe et al. (2020) reported a significant correlation between high alpha power and increased alpha band connectivity on preoperative EEG and the subsequent development of postoperative delirium. Additionally, Ha et al. (2020) reported what they believe to be an EEG complexity measure that predicts postoperative attention deficits. While useful in clinical research, traditional EEG-monitoring modalities are not practical in the routine preoperative anesthetic
assessment of older surgical patients related to cost, time, and technical skill limitations (Inouye et al., 2014; Mulkey et al., 2018; Mulkey et al., 2019).

Delirium detection, especially early detection, is critical because prolonged duration of delirium is associated with increased treatment difficulty (Mulkey et al., 2019). EEG-based delirium assessments can often identify a delirious brain state prior to the presentation of clinical signs and symptoms (Mulkey et al., 2019). Mulkey et al. (2019) is evaluating the clinical utility of a novel limited lead EEG device, Ceribell, for detecting delirium in ICU patients due the limited clinical utility of gold-standard delirium assessment tools used in research (e.g., CAM). When CAM-ICU is incorporated into routine clinical practice, less than 50% of ICU patients with delirium are diagnosed (Soja et al., 2008). This may be due to the extensive and recurrent training required to maintain high inter-rater reliability and the significant staff turnover reported among ICU nurses (Milkey et al., 2019). Similar training and staff turnover challenges would likely be present in post-surgical units attempting to incorporate CAM for the routine assessment of postoperative delirium. For these reasons, Inouye et al. (2014) advocate for further investigation into the clinical use of novel EEG devices (e.g., quantitative and spectral EEG) as they may have clinical utility, but “their performance characteristics need further investigation” (p. 917).

Preoperative anesthesia assessments include a detailed review of cardiovascular and respiratory function (e.g. assessing metabolic equivalency to task (METs), auscultating the heart and lungs, and reviewing pertinent laboratory values). However, minimal assessment of anesthesia’s primary target, the brain, is routinely completed. As previously noted, Crosby et al. (2011) stressed this concern:
…that we currently make no effort to identify [older patients with a vulnerable brain state] preoperatively is an embarrassing state of affairs considering that the brain is a principal target of general anesthetic agents, the field of anesthesiology champions thorough preoperative evaluation, and perioperative cognitive morbidity in the elderly is so common and costly (p. 1267).

One major barrier to completing a more thorough preoperative neurocognitive assessment is that no rapid, easily-administrable, valid, reliable, automatically scored, and cost-efficient assessment of neurocognitive function that is void of language, cultural, and education bias is currently available to anesthesia providers for routine clinical use.

EEG-based P300 AEPs as neurobiomarkers might enable anesthesia providers to better assess baseline neurocognitive function in older surgical patients prior to surgery and anesthesia if the device and process used to conduct these assessments is practical in regards to the skills and equipment required to perform the test and interpret the results. Objective assessments, such as P300 AEPs, may detect mild or even subsyndromal cognitive impairments that are currently missed in a subset of patients by clinically utilized cognitive assessment tools (e.g., MoCA, Mini-Cog©, and CAM) as well as perioperatively track the progression of patients’ cognitive status relative to their baseline to determine if, and when, postoperative neurocognitive alterations occur.

**Novel Point-of-Care EEG Assessment System**

The WAVi Medical™ system (Boulder, CO) is a patented, novel, noninvasive, FDA-cleared POC EEG hardware and software application platform designed to rapidly perform EEG-based neurocognitive assessments (WAVi, 2019). See Appendices D, E, and F. The WAVi Medical™ system is a unique device that utilizes innovative saline moistened fabric electrodes,
eSocs™, to transmit and record the brain’s electrical activity and an integrated artifact detection software system that enhances test-retest and inter-rater reliability when conducting POC EEG-based assessments. The WAVi Medical™ system has been successfully used to assess baseline cognitive function and track changes over time in individuals following traumatic brain injury (Grover et al., 2017; Clayton et al., 2020). The system is currently being used as a neurocognitive assessment tool in a National Institutes of Health (NIH)-funded chronic pain study (National Institutes of Health, 2018). The system is also being utilized to measure onset and progression of cognitive decline in preclinical Alzheimer's patients at the University of Texas at Dallas (Clinicaltrials.gov, 2018). There is a gap in the anesthesia literature in that the potential clinical utility of the WAVi Medical™ system as a neurocognitive assessment tool has never been evaluated in the perioperative setting.

The WAVi Medical™ system consists of the following major components: headsets, solutions, electronics, accessories, and documentation systems. Table six presents a detailed list of the WAVi Medical™ system components. Three headset sizes (e.g., small, medium, and large) are included with the WAVi Medical™ system to accommodate a wide range of head circumferences (WAVi, 2019). The headset is made of a soft double layered closed-cell resin-based foam that easily flexes to the contour of an individual’s head (Oakley, 2018). Figure 5 shows the WAVi Medical™ EEG Headset. Receptacles are located throughout the headset and positioned in the locations of a standard 10-20 EEG montage. The standard 10-20 EEG montage is depicted in Figure 6. An electrical conduction strip is located within the headset between the two layers of foam. Unique to the WAVi Medical™ system, single-use eSocs (i.e., ~ 1in long x 0.25in diameter plastic, fabric-covered electrodes) moistened with a 0.9% sodium chloride
solution (i.e., normal saline) are inserted into the receptacles just prior to performing an assessment. Figure 7 depicts an image of eSocs.

Table 6

**WAVi Medical™ System Components**

<table>
<thead>
<tr>
<th>Headsets</th>
<th>Electronics</th>
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<tbody>
<tr>
<td>- Small headset</td>
<td>- Laptop computer with WAVi™ desktop software</td>
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<tr>
<td>- Medium headset</td>
<td>- USB mouse</td>
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<tr>
<td>- Large headset</td>
<td>- Electronic processing unit (EPU)</td>
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<td></td>
<td>- USB mini-B cable for EPU</td>
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<tr>
<td></td>
<td>- Headphones</td>
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<tr>
<td></td>
<td>- 3.5mm auxiliary cable for headphones</td>
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</table>

<table>
<thead>
<tr>
<th>Accessories</th>
<th>Solutions</th>
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<tbody>
<tr>
<td>- Portable bag</td>
<td>- NuPrep® skin prep gel</td>
</tr>
<tr>
<td>- Headset racks</td>
<td>- Conduction cream</td>
</tr>
<tr>
<td>- eSocs™</td>
<td>- 0.9% sodium chloride saline solution</td>
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<tr>
<td>- eSocs™ trays</td>
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<tr>
<td>- Sizing ribbon</td>
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<tr>
<td>- Syringes</td>
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<tr>
<td>- Blunt needles</td>
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<td>- Towels and washcloths</td>
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<td>- Magnetic ear electrodes</td>
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<td>- Alcohol cleaning wipes</td>
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<tr>
<td>- Diamond bands</td>
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<td>- Hand sanitizer</td>
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<th>Documentation Systems</th>
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<td>- Instruction manual</td>
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<td>- Quick setup and scan guide</td>
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<td>- Cloud instruction manual</td>
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Figure 5

EEG Headset: WAVi Medical$^{TM}$ System (Boulder, CO)

Note: The soft closed-cell resin-based headset used for conducting EEG-based neurocognitive assessments with the WAVi Medical$^{TM}$ system, size small.

Figure 6

Standard 10-20 EEG Montage

Note: The standard 10-20 EEG montage used for EEG electrode placement.
Note: Three dry eSocs (left) and a tray of 20 saline moistened eSocs (right) used to conduct the electrical EEG signal from the participant’s scalp to the WAVi Medical™ headset.

The use of saline-moistened eSocs eliminates the need for metal electrodes to be secured next to the scalp or the need for large amounts of conduction gel to be applied (Oakley, 2018).

Saline soaked eSocs serve as the conduction mechanism for electrical energy to be transferred from the patient’s scalp to the metallic rings located around each receptacle. Figure 8 shows an eSoc inside a metallic ring of the WAVi Medical™ EEG Headset.

**Figure 8**

*WAVi Medical™ eSoc Inside the Metallic Ring of a Headset Receptacle*

Note: An eSoc placed inside the metallic ring of a headset receptacle with the blue end facing the adjustment bands on the outside of the headset and the white end pointing inward.
These metal rings connect to an electrical conduction strip, embedded within the two layers of closed-cell resin-based foam, that conducts the electrical signal to the electrical processing unit (EPU).

The EPU, which amplifies and filters the electrical signal, is connected to the laptop computer via a universal serial bus (USB) mini-B cable to capture the electrical signal and display the graphed EEG waveforms in the WAVi Medical™ desktop software application. WAVi-based neurocognitive scan assessments are completed in accordance with the WAVi Instruction Manual Version 0.9.8.17 (see Appendix E). All investigators performing neurocognitive assessments for the data source study, “Perioperative Brain Health” – IRB HM20019839, with the WAVi Medical™ system completed three online competency-based training modules: 1) Kit Components and Set Up, 2) Headset Contact, and 3) Running the P300 Protocol. Figure 9 depicts a screenshot from one of the online competency-based training modules.

**Figure 9**

*Online Competency-based Training Module 1*

Note: A screenshot from WAVi Medical™’s first competency-based training module: Kit Components and Set Up.
In addition to the online training, one of the data source study’s investigators traveled to WAVi Medical™, Boulder, CO for in-person training on the device and was approved by the device manufacturer to train research assistants. Research assistants successfully completed a two hour in-person, proctored, simulated WAVi Medical™ setup, preparation, and P300 protocol training as well as at least two proctored, clinical evaluations of their ability to setup, prepare, and administer the P300 protocol with the WAVi Medical™ device.

Performing an EEG assessment with the WAVi Medical™ platform is a four step process: 1) equipment set up, 2) participant preparation, 3) donning the headset, 4) performing the assessment (WAVi Medical™, 2017). To set up the WAVi Medical™ system, an investigator fills one 5cc syringe with 0.9% saline and one 5cc syringe with electroencephalogram (EEG) conduction cream (WAVi Medical™, 2017). The investigator opens one tray of 20 WAVi™ eSocs and pours approximately 25ml of normal saline over the eSocs in the tray. The WAVi™ desktop application is accessed on a secure, password protected study laptop (e.g., Dell®, Latitude 3190) in airplane mode (i.e., with WiFi disabled). The investigator connects the EPU to the study laptop via a USB mini-B cable and clicks the +New Patient button in the WAVi™ desktop application.

The participant is asked to remove all hair accessories (e.g., clips, bobby pins, hair ties, barrettes) and earrings from the earlobes (WAVi Medical™, 2017). The participant’s earlobes are exfoliated using NePrep® skin prep gel, and a paper towel is provided to clean any residual NuPrep® off of their earlobes and fingers. The participant’s head circumference is measured using a sizing ribbon (i.e., a flexible plastic measuring tape with predefined markings) to identify the appropriate size headset (e.g, small, medium, or large) for the participant. The investigator places the saline moistened eSocs into the headset receptacles with the blue ends facing the
flexible rubber diamond-shaped adjustment bands and the white ends pointing inward to make contact with the participant’s scalp.

Immediately prior to the participant in donning the headset, the investigator places ~0.5cc of conduction cream on each of the patient’s earlobes, opens the heart rate variability ear clips, and gently closes one clip onto each of the participant’s earlobes. The investigator then assists the participant in placing the headset onto the head in a manner similar to wearing a baseball cap. The investigator ensures optimal headset placement on the participant's head by centering the heart shaped opening at the front of the headset over the participant’s nasion (i.e., bridge of the nose). The heart rate variability ear clips are then connected to the EPU, and the EPU is connected to the laptop computer. A pair of soft, cushioned headphones are placed on top of the headset over the participant’s ears and connected to the EPU. The headset is then visually inspected to ensure that the white tips of the eSocs make contact with the participant’s scalp. If poor scalp contact is identified, the investigator augments eSocs with poor contact by repositioning the headset, gently brushing a small amount of hair away from any eSOCs with poor contact (WAVi Medical™, 2017). The investigator then clicks the +Headset Contact button in the desktop application and inspects for adequacy of the acquired electrical signal from all 20 electrode sites. Sites with sufficient scalp contact and adequate electrical signal are highlighted as yellow or green in the desktop application, sites with a poor signal that require contact adjustment are highlighted red. Figures 10 and 11 show screenshots of the software’s contact feedback system. Visual inspection and electrode augmentation steps, such as applying a small amount of either saline or conductive cream underneath eSoc sites with a poor signal (i.e., those highlighted red), are repeated until an adequate signal is confirmed at all sites (WAVi Medical™, 2017). This process can be completed in less than five minutes.
**Figure 10**

*Desktop Application Electrode Contact Assessment Page--Good Contact*

Note: Electrode sites with sufficient scalp contact and adequate electrical signal are highlighted as yellow or green.

**Figure 11**

*Desktop Application Electrode Contact Assessment Page--Poor Contact*

Note: Electrode sites with sufficient scalp contact and adequate electrical signal are highlighted as yellow or green, sites with poor contact are red, and sites that that are yet to be assessed are gray.
To perform a neurocognitive assessment, the investigator ensures that the computer mouse is located under the participant’s dominant hand and initiates the "WAVi Performance" protocol within the desktop application (WAVi Medical™, 2017). The WAVi Performance protocol consists of a series of 3 EEG-based neurocognitive assessments: 1) a one-minute baseline eyes closed raw-wave EEG assessment, 2) a four-minutes eyes closed P300 assessment, and 3) a one-minute eyes open tracking assessment. Figure 12 shows an individual participating in neurocognitive assessment, and Figure 13 displays a screenshot of the WAVi Medical™ software during a one-minute eyes open tracking protocol.

**Figure 12**  
*Person Participating in Neurocognitive Assessment*

The WAVi Medical™ system is designed to automatically detect and report artifact in the EEG signal. Artifact is an erroneous EEG signal derived from extra-neural sources (e.g., patient movement). Artifact is indicated by the red and blue coloration on EEG waveforms and as red highlighting over respective sites on the 10-20 montage map. Figure 13 illustrates this artifact detection as red and blue coloring of artifact in the EEG signal.
One neurocognitive assessment attainable with the WAVi Medical™ system is the previously validated auditory P300 AEPs. To perform the four-minutes eyes closed P300 assessment using the WAVi Medical™ system, the investigator explains the auditory P300 Eyes Closed test to the participant: "During the test you will hear two different audible tones, a common low-pitched tone and a rare high-pitched tone. When you hear the rare, high-pitched tone, click the mouse button." The investigator provides the participant with a brief, < 30 second practice session and then selects the "P300 Eyes Closed Protocol" within the WAVi Medical™ desktop application. During the test, the participant is presented with 200 baseline (i.e., low-pitched) tones and 40 oddball (i.e., high-pitched) tones over four minutes. Following the test, EEG data is reviewed by the investigator for signal quality. If data quality is acceptable, the test is complete. If data quality is unacceptable, the test is repeated one additional time.

P300 event-related evoked response tests can be used as a neurophysiological marker for even mild neurocognitive disorders (Levada et al., 2016). These assessments utilize an oddball
paradigm to evaluate the brain’s response to a novel stimulus (van Dinteren et al., 2014). The term “oddball paradigm” refers to the presentation of a randomly interspersed (i.e., oddball) auditory stimulus (e.g., a high-pitched tone) presented within a series of background baseline auditory stimuli (e.g., low-pitched tones) (van Dinteren et al., 2014). Healthy brains process and respond to the oddball stimulus, or high-pitched tone, differently than unhealthy brains. When a healthy brain is presented with an oddball stimulus, the amplitude (i.e., size) of graphed waveforms of the brain’s electrical activity are expected to be larger than those produced by an unhealthy brain, and the latency (i.e., a graphed representation of the time required for signal conduction among brain cells) is expected to be shorter.

Brain power and cognitive resources are associated with signal amplitude (i.e., power in microvolts) on EEG (van Dinteren et al., 2014). Brain speed and efficiency are associated with signal latency (i.e., delay in milliseconds) on EEG (van Dinteren et al., 2014). The graphed waveform changes identified on EEG following the presentation of an oddball stimulus often present approximately 300 milliseconds after the stimulus is presented. For this reason, these waveforms are referred to as P300 waveforms and the assessment as a P300 auditory evoked potential. However, the waveform change may present with varying degrees of latency 200-500 milliseconds after an auditory stimulus is presented depending on an individual’s age, gender, and brain health (Sur & Sinha, 2009; Uvais et al., 2018). Additionally, the amplitude (i.e., size) of the P300 waveform varies with cognitive resources (Levada et al., 2016). Such variations in amplitude and latency of the P300 waveform are associated with alterations in brain health (Levada et al., 2016; Melynyte et al., 2018; Sur & Sinha, 2009; Uvais et al., 2018).
P300 Waveforms

The P300 waveform is a large positive waveform extracted from the EEG signal in response to an oddball paradigm during an auditory-evoked response test (van Dinteren et al., 2014). An auditory evoked response oddball paradigm consists of the presentation of a randomly interspersed oddball target auditory stimulus (e.g., high-pitched tone) within a series of common background baseline auditory stimuli (e.g., low-pitched tones). Even though the P300 waveform represents a positive change in amplitude from baseline, the waveform is classically graphed as a downward deflection from baseline. See Figures 14-17.

Figure 14

Four-minute Eyes Closed P300 Assessment

Note: The black vertical line overtop the EEG waves (left side of image) denotes the presentation of a common auditory stimulus. The redline overtop the EEG waves denotes the presentation of an oddball auditory stimulus. The green line overtop the EEG waves denotes the participant’s physical response (i.e., mouse button click). Artifact is identified as red and blue coloration of the FP1 and F8 waveforms (left side of image).
Figure 15

Illustrated Event Related Response Test, Baseline Waveform, & P300 Waveform

Note: An illustrated comparison of the differences observed in the P300 waveform following the presentation of an oddball stimulus versus a background stimulus. Image adapted from van Dinteren et al. (2014).

Figure 16

Average P300 Waveform Captured at a Single Site (Pz)

Note: A screenshot of data review following a four-minutes eyes closed P300 assessment.
Figure 17

Average P300 Waveforms Captured at All 10-20 EEG Montage Sites

Note: FP1 and FP8 do not display waveforms in this image because the software’s auto artifact detection system identified an insufficient number of adequate P300 waveforms at the FP1 (8/40) and F8 (5/40) locations.

P300 Changes Associated with Altered Neurocognitive States

Changes in the amplitude and latency of the P300 waveform are associated with altered neurocognitive states (Polich, 2004; Sur & Sinha, 2009; Clayton et al. 2020). Specifically, reduced P300 amplitude and prolonged P300 latency have both been associated with neurobiological vulnerabilities including mild cognitive impairment, Alzheimer’s disease, and dementia (Egerházi et al., 2008; Hedges et al., 2016; Medvidovic et al., 2013; Uvais et al., 2018; Yilmaz et al., 2017).

Yener et al. (2013) demonstrated that event-related evoked response tests can be used to detect mild cognitive impairment. Krishnamurthy et al., (2019) reported that auditory evoked P300 tests can be used to identify subclinical cognitive impairment in patients with chronic obstructive pulmonary disease (COPD). Yilmaz et al. (2017) demonstrated that auditory evoked
P300 tests provide a diagnostic tool for mild cognitive impairment in patients with Parkinson’s disease. Patients with mild cognitive impairment demonstrated prolonged P300 latency and often (i.e., 35% of the time) a total loss of the P300 amplitude relative to patients without mild cognitive impairment (Yilmaz et al., 2017). Egerházi et al., (2008) reported that P300 latency was significantly prolonged in patients with mild cognitive impairment with cerebral atrophy as well as in patients with both vascular and Alzheimer’s dementia.

Parra et al. (2012) reported that P300 is a “very useful method for the preclinical assessment of [Alzheimer’s disease], particularly in populations with low socioeconomic and educational levels.” Meta-analysis and meta-regression of 646 participants from twenty P300 studies identified a reduced P300 amplitude in participants with Alzheimer’s disease versus healthy controls (Hedges et al., 2016). Additionally, recent meta-analyses identified that P300 latencies were prolonged in patients with mild cognitive impairment, relative to healthy controls, and prolonged in patients with Alzheimer’s disease relative to patients with mild cognitive impairment (Gu & Zhang, 2017; Howe et al., 2014; Jiang et al., 2015; Morrison et al., 2018). This data indicates that auditory evoked P300 tests may have clinical utility as an identification tool, differential biomarker, and possibly predictive metric for the progression of neurocognitive impairments (Gu & Zhang, 2017; Howe et al., 2014; Jiang et al., 2015; Morrison et al., 2018).

**Montreal Cognitive Assessment (MoCA)**

MoCA version 8.1 (see Appendix A) is considered to be the gold standard rapid screening tool for identifying mild cognitive impairment (Nasreddine et al., 2005). MoCA is a single page assessment instrument used to evaluate a participant’s performance on a battery of neurocognitive tests. The assessment takes approximately 15 minutes to administer. The exact duration of the assessment depends on how long it takes a participant to complete each test. The
neurocognitive tests included in MoCA are: three visuospatial drawing tests, one animal naming test, one word list memory test, three attention related tests (e.g., digits, letters, and subtraction), two language tests, one abstraction test, one delayed recall test, and one orientation test. During the assessment, the administrator remains present with the participant to record and interpret the results of each test in real time. If the participant completes a given test without difficulty, they receive a point value for that test. Point values for each test range from one to six. The participant’s final MoCA score is the summation of all individual test scores. The final MoCA score ranges from 0-30 with higher scores indicating a higher level of cognitive function.

A MoCA score between 26-30 indicates normal cognitive function (Nasreddine et al., 2005). A MoCA score between 18-25 indicates mild cognitive impairment. This range is classified as a MoCA severity level one. A MoCA score 10-17 indicates moderate cognitive impairment. This range is classified as a MoCA severity level two. A MoCA score below 10 indicates severe cognitive impairment. This range is classified as a MoCA severity level three. Styra et al. (2019) reported that MoCA scores ≤ 15 are predictive of POD. P300 waveform deformities (e.g., prolonged latency and decreased amplitude) reportedly correlate with MoCA in patients with idiopathic inflammatory-demyelinating diseases (Zeng, et al., 2017). However, no relationship has been established between P300 and MoCA in the perioperative setting.

Nasreddine et al. (2005) reported a 90% sensitivity and 100% specificity for MoCA to diagnose mild cognitive impairment in older persons in the research setting when evaluating Caucasian older adults. However, Berger et al. (2018) reported that there is insufficient data to report sensitivity and specificity for MoCA in the perioperative setting and that MoCA has an inherent education bias. Rossetti et al. (2017) identified that several components of the MoCA and previously established cut-off points for cognitive impairment are not well suited for African
Americans. In a sample of over 1,000 community-dwelling African Americans with an average age of 49 years and no subjective cognitive complaints, the mean MoCA score was 22 (Rossetti et al., 2017). In this sample, 72% of participants were unable to complete the cube drawing task, 66% of participants recalled fewer than 4/5 delayed free recall words, 63% were unable to complete the sentence repetition task, and 45% failed the abstraction portion of the assessment (Rossetti et al., 2017). These factors all present challenges for the use of MoCA as a routine clinical preoperative neurocognitive screening tool as MoCA may underestimate neurocognitive function in African American patients (i.e., MoCA scores may be lower for African Americans than for Caucasians with an equivalent level of cognitive function).

MiniCog©

MiniCog© (see Appendix B) is a brief neurocognitive screening tool with a two-part empirical scoring algorithm: a 3-word recall and a clock drawing test (Borson et al., 2003). The MiniCog© is administered in approximately three minutes and is used to detect cognitive impairment in older adults. Administration of the MiniCog© is a simple four step process:

1) Gain the patient’s attention by stating “What we’re going to do next will take some concentration. Ready?”

2) Initiate the 3-word recall task by saying “I am going to say three words that I want you to remember now and later. The words are banana, sunrise, chair.”

3) Provide a sheet of paper with a circle already drawn for the patient (See Appendix B) and ask the participant to “Please draw a clock in the circle…put all the numbers in the circle.” After numbers have been placed in the clock, say “Now set the hand to show ten past eleven.”

4) Say “What were the three words I asked you to remember?”
The Mini-Cog© is scored on a scale of 0-5. One point is awarded for each of the three words that the participant recalls. Two points are awarded for a normal clock, and no points are awarded for an abnormal clock. A normal clock presents with all numbers (1-12) placed in the correct order and direction, one hand pointing to the number 11 and one hand pointing to the number two. A score $\geq 3$ signifies a reduced probability of dementia but does not exclude cognitive impairment (Borson, 2021). Mini-Cog© is a validated screening tool for both dementia and mild cognitive impairment in older participants (Borson et al., 2003; Steenland et al., 2008). However, this simple assessment tool provides only a rough estimate of gross cognitive dysfunction. Mini-Cog© interpretation guidelines state “[a] total score of 3, 4, or 5 indicates lower likelihood of dementia but does not rule out some degree of cognitive impairment. The Mini-Cog© is not a diagnostic test for Alzheimer’s disease or any other dementia or cause of cognitive impairment. Diagnosis of brain disorders that cause cognitive impairment requires a medical examination and additional examinations” (Borson, 2021).

Confusion Assessment Method (CAM)

CAM is a validated tool used by non-psychiatric providers (e.g., bedside nurses) to screen patients for POD by assessing for: acute onset, inattention, disorganized thinking, altered consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor retardation, and altered sleep-wake cycles (Inouye, 2003). Inouye (2003) recommends that CAM assessments be based upon a standardized interview between the participant and the investigator. Inouye (2003) suggests the administration of Mini-Cog© be used as the standardized interview. CAM is considered to be the gold standard screening tool for delirium identification (Inouye, 2003). CAM has been used for delirium screening in over 250 studies and reportedly has a 94-100% sensitivity and 90-95% specificity for identifying delirium in the research setting (Inouye,
However, in routine clinical practice, less than 50% of ICU patients with delirium are identified by CAM (Soja et al., 2008). This may be due to the extensive and recurrent training required to maintain high inter-rater reliability and the significant staff turnover reported among ICU nurses (Milkey et al., 2019). Similar limitations could be expected if routine postoperative CAM assessments were performed on postsurgical recovery units.

Chapter Summary

Perioperative neurocognitive disorders are a major brain health related concern for older surgical patients (American Society of Anesthesiologists, 2019; Berger et al., 2018; Mahanna-Gabrielli et al., 2019). Some researchers believe these disorders to be the result of neurobiological alterations sustained from surgery and anesthesia, yet others believe them to be a post hoc, ergo propter hoc misattribution fallacy (Avidan & Evers, 2016; Berger et al., 2018; Mahanna-Gabrielli et al., 2019; Jin et al., 2020). A decade after Crosby et al. (2011) lamented “… that we currently make no effort to identify [older patients with a vulnerable brain state] preoperatively…” anesthesia providers are beginning to incorporate questionnaire-based neurocognitive assessments into the preanesthetic assessment at some academic medical centers (p. 1267; Mahanna-Gabrielli et al., 2019; Decker et al., 2020). However, none of these tools are routinely used for perioperative neurocognitive assessment due to validity, reliability, and practicality concerns (Berger, et al., 2018).

POD, the first acute event of neurocognitive impairment following surgery and anesthesia, is the most prevalent complication experienced by older adult patients (American Geriatrics Society, 2015; American Society of Anesthesiologists, 2019). POD distresses patients, their loved ones, and care providers, and is associated with inferior functional recovery and increased healthcare spending (Hernandez et al., 2017; Hshieh et al., 2017; Inouye et al., 2014;
Baseline cognitive function is a strong, independent predictor for POD in older surgical patients, and POD is believed to be preventable in up to 40% of patients (Culley et al., 2017; Siddiqi et al., 2016). Perioperative patient outcomes may be enhanced by improving baseline neurocognitive assessments in order to better identify preexisting neurocognitive impairment and risk-stratify patients. EEG-based auditory evoked P300 tests may have clinical utility as an identification tool, differential biomarker, and possibly predictive metric for the progression of perioperative neurocognitive impairments (Gu & Zhang, 2017; Howe et al., 2014; Jiang et al., 2015; Morrison et al., 2018).

Over 50% of patients who experience POD present with signs of delirium on postoperative day one (Iamaroon et al., 2020; Lin et al., 2016). The most common presentation of delirium, the hypoactive form, is more challenging to identify in clinical practice and often goes undiagnosed (Collins, 2010; Hosker & Ward, 2017). When gold-standard delirium assessment tools (e.g., CAM) are incorporated into routine clinical practice, less than 50% of patients with delirium are diagnosed (Soja et al., 2008). Early delirium detection is critical because prolonged duration of delirium is associated with increased treatment difficulty (Mulkey et al., 2019). EEG-based neurocognitive assessments can reportedly identify subsyndromal delirium (i.e., neurocognitive changes that portend delirium) prior to the presentation of clinical signs and symptoms (Mulkey et al., 2019).

However, traditional EEG assessment modalities are not easily incorporated in routine clinical practice (Inouye et al., 2014; Mulkey et al., 2018; Mulkey et al., 2019). The WAVi Medical™ system is an FDA-cleared POC EEG hardware and software system designed to rapidly perform EEG-based P300 AEP neurocognitive assessments (WAVi, 2019). Neurobiomarkers obtainable with this device may have clinical utility for identifying, predicting,
and tracking perioperative neurocognitive disorders. However, the utility of the WAVi Medical™ system has never been evaluated in the perioperative setting.
Chapter 3: Theoretical Framework

“The secret of quality is love.” - Avedis Donabedian

Chapter Overview

Chapter three presents this study’s guiding theoretical framework, Donabedian’s Theoretical Model for Evaluating the Quality of Medical Care. The chapter begins with a brief overview of the origin and history of Donabedian’s model. The suitability of the model for this study is discussed. Studies applying and validating the Donabedian model in the perioperative setting are identified.

Introduction

Over 50% of surgical procedures performed in the United States (U.S.) are performed on patients over the age of 65 years (Yang et al., 2011). A significant number of these patients may subsequently develop postoperative delirium (POD). POD, a state of disorganized thinking and inattention, complicates the recovery process and is associated with increased length of hospitalization, increased morbidity and mortality, progression to delayed or incomplete neurocognitive recovery, and the subsequent development of dementia (Saczynski et al., 2012; Koster et al., 2012; Hshieh et al., 2017; Sprung et al., 2017; Aranake-Chrisinger & Avidan, 2017). The American Society of Anesthesiologists’ Perioperative Brain Health Initiative advocates for research aimed at discovering novel POD identification, mitigation, and prevention strategies (American Society of Anesthesiologists, 2019). No rapid, reliable, practical, sensitive and specific assessment of neurocognitive function currently exists to preoperatively identify at-risk patients, recognize POD in the early postoperative period, or track POD in older surgical
patients. This study is designed to analyze EEG-based neurocognitive assessment data captured in the perioperative setting with an innovative POC EEG hardware and software system, WAVi Medical™ to evaluate the potential clinical utility of neurobiomarkers obtained with the device. These neurobiomarkers may one day be used to guide the clinical care of older surgical patients and reduce the incidence and/or severity of perioperative neurocognitive disorders (e.g., POD).

The study was guided by Donabedian’s Theoretical Model for Evaluating the Quality of Medical Care (Donabedian, 2005). Donabedian’s care model is the most commonly used theoretical framework for evaluating the quality of health care services (Ayanian and Markel, 2016). Donabedian first published his seminal work in The Milbank Quarterly, a multidisciplinary journal of population health and health policy, in June 1966 (Berwick & Fox, 2016). The paper was reprinted verbatim in the same journal in 2005 (Berwick & Fox, 2016). Donabedian (2005) put forth three concepts (structure, process, and outcome) as guiding principles for quality improvement. These concepts now serve as the constructs of Donabedian’s theoretical model. The three key domains of Donabedian’s quality improvement model are shown in figure 18.

**Figure 18**

*Donabedian’s Theoretical Model for Evaluating the Quality of Medical Care*

| Structure | Process | Outcome |

Donabedian’s (1966) theoretical model for evaluating the quality of medical care was a good fit for this study because it is descriptive, explanatory, accurate, practical, simple, consistent, and acute (Goes & Simon, 2012).
Descriptive & Explanatory

Goes and Simon (2012) state that a theory should explain the “Who? What? When? Where? How? [and] Why? about a situation or phenomenon” (p. 2). Donabedian’s (2005) model explains all six questions in regards to this study. Three of these questions (i.e., Who?—older surgical patients When?—perioperative period Where?—PACE and post-surgical follow-up) are addressed within the construct of structure. What—method of neurocognitive assessment—P300 versus MoCA is addressed by the construct process. Why— to identify novel neurocognitive assessment tools and biomarkers for predicting, identifying, and tracking perioperative brain health in older surgical patients—can be categorized under the construct outcome.

Accurate

Accuracy can be evaluated by “investigating what a variety of experts say regarding the theory” (Goes and Simon, 2012, p. 2). Donabedian’s (2005) model has been applied, tested, retested and referenced by researchers from a variety of disciplines for over fifty years (Berwick & Fox, 2016). Within that time frame the model’s creator authored four books on quality assessment in medical care including: 1) The Definition of Quality and Approaches to Its Assessment, 2) The Criteria and Standards of Quality, 3) The Methods and Findings of Quality Assessment and Monitoring: An Illustrated Analysis, and 4) An Introduction to Quality Assurance in Health Care (Berwick & Fox, 2016).

Practical

Multiple real-world applications of Donabedian’s (2005) model are identifiable in the literature. At least six studies incorporated the model to guide perioperative research. Rose et al. (2019) applied the model to guide an integrative review of the literature to identify best practices for postoperative patient handoff. Specifically, the authors used Donabedian’s model to organize
and synthesize seventeen articles on information transfer during patient handoff from surgical and anesthesia teams to the postoperative care unit (PACU) teams. Figure 19 shows Rose et al.’s (2019) use of the model.

**Figure 19**

*Patient Handoff Structures, Processes, & Outcomes Based on Donabedian’s Model*

Note: Image adapted from Rose et al. (2019).

Jeffcott et al. (2009) and Gardener et al. (2014) also employed Donabedian’s model to evaluate quality of care of patient handoff and other nursing services.

Centurion et al. (2018) applied the model to identify the minimum standard of care when performing surgery with limited resources following natural disasters in low- and middle-income countries. The authors identify that Medécins Sans Frontières (MSF) (i.e., Doctors Without Borders) has been providing surgical care services in low- and middle-income countries for 45 years. Over this time, the organization has utilized Donabedian’s model to measure the quality of these services in various locations around the globe. As an example, MSF evaluates human resources, infrastructure (e.g., water and electricity supply), biomedical devices, and the supply of medications using the structural component of Donabedian’s model (Centurion et al., 2018).
Moore et al. (2015) validated the model for assessing quality of care improvement in trauma care services in a multicenter retrospective cohort study. Prior to Moore et al.’s (2015) study that statistically evaluated correlation between process and outcomes, Donabedian’s model had already been widely adopted by trauma care providers to guide quality improvement projects. The authors identified that trauma centers with appropriate structures tend to have strong clinical processes that positively impact patient outcomes (Moore et al., 2015).

Tsai et al. (2013) used Donabedian’s model to guide their investigation of the readmission rates of surgical patients. The authors incorporated Donabedian’s structure, process, and outcome components of quality of care to investigate 30-day readmission rates of 479,471 Medicare patients from 3,004 different hospitals following a variety of surgical procedures including: coronary artery bypass graft (CABG), pulmonary lobectomy, endovascular abdominal aortic aneurysm repair (EVAR), open abdominal aortic aneurysm repair (AAA), colectomy, and hip replacement.

Birkmeyer et al. (2004) adopted the Donabedian model to evaluate quality of surgical care services. The authors noted that hospitals are increasingly under pressure to evaluate and demonstrate quality of care as it becomes increasingly apparent that patient outcomes vary nationally by surgeon and hospital. Noting the wide variation of quality improvement metrics used in prior studies, the authors sought to report on the potential advantages and disadvantages of each after classifying metrics as either structure, process, or outcome in an effort to identify a focus for future investigation. Figure 20 depicts an example of how these authors incorporated the model.

Hannan et al. (2001) employed the model to guide a retrospective cohort investigation of outcomes following carotid endarterectomy surgery among 3,644 patients. As a result of the
Figure 20

Example of Structures, Processes, & Outcomes of Surgical Care

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<tr>
<th></th>
<th>Structure</th>
<th>Process</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Examples</td>
<td>Procedure volume</td>
<td>Perioperative β-blockers in high-risk surgical patients</td>
<td>Morbidity and mortality rates</td>
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<tr>
<td></td>
<td>Fellowship-trained surgeons</td>
<td>Use of internal mammary graft during coronary artery bypass graft</td>
<td>Functional health status</td>
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<td></td>
<td>“Closed” intensive care units</td>
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<td>Patient satisfaction</td>
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<td>Cost</td>
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<tr>
<td>Primary</td>
<td>Expedient, inexpensive proxies of surgical outcomes</td>
<td>Reflect care that patients actually receive—may seem “fairer” to providers</td>
<td>Buy-in from surgeons—the “bottom line” of what they do</td>
</tr>
<tr>
<td>advantage(s)</td>
<td></td>
<td>Actionable from provider perspective, clear link to quality improvement activities</td>
<td>Outcomes measurement alone may improve outcomes</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Most variables not actionable from provider perspective</td>
<td>Little information about which processes are important for specific procedures</td>
<td>Numbers too small to measure with adequate precision procedure-specific outcomes for most hospitals and procedures</td>
</tr>
<tr>
<td></td>
<td>Imperfect proxies for outcomes—reflect average results for large groups of providers, not individuals</td>
<td></td>
<td>Outcomes measures that are not procedure-specific less useful for purposes of quality improvement</td>
</tr>
</tbody>
</table>

Note: Image adapted from Birkmeyer et al. (2004).

noted variation in practice patterns and patient outcomes, the authors sought to identify which, if any, processes led to superior inpatient outcomes. The authors identified that when a combination of processes (e.g., eversion endarterectomy, protamine, or shunts) were utilized, fewer patients had adverse outcomes (OR=0.42, P=0.006).

Simple

Donabedian’s (2005) unidirectional model is constructed of three simple concepts: structure, process, and outcome. All three constructs are capable of influencing quality of care. For this study, structure remained constant, and alternative processes (i.e., neurocognitive assessment methods) were evaluated to determine if P300 metrics potentially predict, identify, and track an outcome, perioperative neurocognitive disorders (e.g., POD).
Consistent

Both internal and external consistency of Donabedian’s (2005) model have been considered. Internal consistency refers to the inherent logical nature of a theory, and external consistency references a given theory in relation to other theories. Donabedian’s (2005) model is logical in the context of this study. Within a defined and relatively consistent structure, changing a clinical process could logically affect an outcome. Moore et al. (2015) validated the external consistency of the Donabedian model for trauma care. The authors demonstrated statistically significant correlation between a process (e.g., conformity to 15 implemented quality improvement metrics) and two outcomes (e.g., length of stay ($r = -0.27$) and readmission ($r = -0.33$)).

Acute

Goes and Simon (2012) describe an acute theory as one that is able “to provide insight into an otherwise complex problem” (p. 3). Perioperative neurocognitive disorders are quite a complex problem. The causative etiology of POD is unknown and likely multifactorial (Wu et al., 2019). What is known is that baseline cognitive function is a strong, independent predictor for POD in older surgical patients (Adegowa et al., 2018). However, no rapid, reliable, practical, and highly sensitive and specific neurocognitive assessment tool is currently available to anesthesia providers for routine clinical care.

As previously mentioned, Crosby et al. (2011) lamented this problem:

…that we currently make no effort to identify [older patients with a vulnerable brain state] preoperatively is an embarrassing state of affairs considering that the brain is a principal target of general anesthetic agents, the field of anesthesiology champions
thorough preoperative evaluation, and perioperative cognitive morbidity in the elderly is so common and costly (p. 1267).

To address this gap, this study employed Donabedian’s (2005) model.

**Application of Donabedian’s Quality of Care Model**

Donabedian’s (2005) model clearly identifies and operationalizes three categories for consideration when seeking to improve patient outcomes in health care research. Structure refers to the physical and organizational characteristics where healthcare occurs. In this study, the structure referenced the perioperative setting (i.e. specifically, the preoperative assessment, communication, and education (PACE) clinic and the post anesthesia care unit (PACU)). Process refers to the manner in which a system or procedure works to provide a desired outcome, and outcome refers to the impact an intervention has on patients. In this study, the process-outcome relationship being investigated was the utilization of EEG-based P300 neurocognitive metrics versus best medical practice (e.g., MoCA) to identify and track perioperative neurocognitive states in older surgical patients. See Figure 21.

**Figure 21**

*Specific Structures, Processes, & Outcomes for This Study*

<table>
<thead>
<tr>
<th>Structure</th>
<th>Process</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| - Preoperative assessment, communication, and education (PACE) clinic<br> - Presurgical unit (PSU)<br> - Operating room (OR)<br> - Post anesthesia care unit (PACU)<br> - Post-surgical follow-up | - P300 amplitude<br> - P300 latency<br>  
  \[ \text{versus} \]  
  \[ \text{MoCA} \] | - Postoperative delirium (POD)<br>  
  - Preoperative prediction of POD<br>  
  - Postoperative identification of POD |
Specific Aims & Hypotheses

Specific Aim #1: Evaluate the ability of participants’ preoperative baseline P300 latency (i.e., brain speed) and P300 amplitude (i.e., brain power) to predict participants’ cognitive function. This study used regression to understand whether auditory P300 amplitude (in microvolts) and auditory P300 latency (in milliseconds) predict cognitive function among older surgical patients as assessed by MoCA. Each variable was considered independently as they measure two separate constructs of neurocognition, namely cognitive resources (i.e., brain power) and cognitive efficiency (i.e., brain speed).

Hypothesis #1: Lower P300 amplitude will be predictive of lower MoCA scores.

Hypothesis #2: Higher P300 latency will be predictive of lower MoCA scores.

Specific Aim #2: Evaluate for group differences in pre- to postoperative P300 AEP change scores (i.e., amplitude (in microvolts) and latency (in milliseconds)) between participants who received two or more potentially neuroprotective multimodal anesthetic adjunct medications (i.e., magnesium, lidocaine, and/or ketamine) versus those who did not.

Hypothesis #3: Participants who received two or more potentially neuroprotective multimodal anesthetic agents will demonstrate a larger positive change in their P300 amplitude, measured as a pre- to postoperative change score in microvolts.

Hypothesis #4: Participants who received two or more potentially neuroprotective multimodal anesthetic agents will demonstrate a smaller degree of prolongation in their P300 latency relative to their baseline, measured as a pre- to postoperative change score in milliseconds.
Chapter Summary

Each year, 50% of surgeries in the U.S. are performed on patients over the age of 65 years (Yang et al., 2011). The most common complication experienced by these patients is POD. POD is a state of confusion and inattention that complicates the recovery process, increases hospital length of stay, increases patients’ morbidity and mortality risk, and escalates health care costs (Saczyński et al., 2012; Koster et al., 2012; Hshieh et al., 2017; Sprung et al., 2017; Aranake-Chrisinger & Avidan, 2017). Improved neurocognitive assessment tools may offer anesthesia providers more detailed information on the state of a patient’s brain throughout the perioperative period. Such information could guide the development of a perioperative brain health protocol to reduce the incidence and severity of POD in older surgical patients.

This study, guided by Donabedian’s Theoretical Model for Evaluating the Quality of Medical Care, was designed to analyze the utility of EEG-based neurocognitive assessment data to perioperatively identify and track neurocognition in older surgical patients. Donabedian’s model was appropriate for this study because the model is descriptive, explanatory, accurate, practical, simple, consistent, and acute in identifying links between practice processes and patient outcomes in the perioperative setting (Birkmeyer et al., 2004; Centurion et al., 2018; Hannan et al., 2001; Moore et al., 2015; Rose et al., 2019; Tsai et al., 2013).
Chapter 4: Methodology

Chapter Overview

The purpose of this study was to explore baseline and postoperative neurocognitive characteristics that may help to establish novel predictive and trend metrics for perioperative neurocognitive assessment in older surgical patients. As a proof-of-concept study, this research primarily sought to identify associations that may be useful in generating hypotheses to guide future research. This study was largely a proof of concept study, due to the small sample size of records available from the data source study, accepting the impact of sample size on statistical conclusion validity. The study evaluated the potential for P300 AEPs to recognize and track perioperative neurocognitive alterations in older surgical patients. The identification, organization, and analysis of study variables was guided by the three constructs of Donabedian’s Theoretical Model for Evaluating the Quality of Medical Care: structure, process, and outcome. Chapter four presents the study’s methodology including: research design, data source, sampling strategy, and study variables. This chapter describes the study’s data management and analysis plans in detail, and concludes with a discussion of assumptions, limitations, and the study’s significance.

Research Design

To evaluate the potential utility of P300 AEPs for assessing and tracking perioperative brain health in older surgical patients, the following methodology was used. The study employed a non-randomized, non-experimental, ex post facto secondary data analysis design to 1) retrospectively compare participants’ P300 AEPs to MoCA scores before surgery and anesthesia
and 2) evaluate for mean group differences in pre- and postoperative change scores between participants who received two or more potentially neuroprotective multimodal anesthetic agents and those who did not. Secondary data analyses explore research questions by using an existing data set (Hulley et al., 2013). Secondary data sources may include electronic medical records, administrative databases, or existing research studies (Hulley et al., 2013). In retrospective studies, investigators begin with a dependent variable and look backward to determine whether or not an association exists between the dependent variable and one or more independent variables (Polit & Beck, 2017). Retrospective designs can be used to identify potentially predictive factors for an outcome (Polit & Beck, 2017).

**Aims & Hypotheses**

This study evaluated two specific aims. The first study aim was to evaluate the ability of participants’ preoperative baseline P300 latency and amplitude to predict participants’ cognitive function as assessed by MoCA. The second study aim was to evaluate for mean group differences in pre- to postoperative P300 AEP change scores between participants who received two or more potentially neuroprotective multimodal anesthetic adjunct medications (e.g., lidocaine, ketamine, and magnesium) versus those who did not. Table seven delineates the study purpose, aims, and hypotheses.

**Data Source**

Data for this study was extracted from the VCU/VCUHS REDCap® database: “Perioperative Brian Health” – PID 22988. Data in this database was collected using a longitudinal, repeated measures design to conduct a prospective observational trial with a set of pretests and multi-observation post-tests. Figure 22 illustrates the data source study’s research design.
Table 7

Study Purpose, Aims, and Hypotheses

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Aims</th>
<th>Hypotheses</th>
</tr>
</thead>
</table>
| Explore baseline and postoperative neurocognitive characteristics that may help to establish novel predictive and trend metrics for perioperative neurocognitive assessment in older surgical patients | **Aim 1**: Evaluate the ability of participants’ preoperative baseline P300 latency and amplitude to predict participants’ cognitive function.  
**Aim 2**: Evaluate for group differences in pre- to postoperative P300 AEP change scores between participants who received two or more potentially neuroprotective multimodal anesthetic adjunct medications versus those who did not. | **H₁**: Lower P300 amplitude will be predictive of lower MoCA scores.  
**H₂**: Higher P300 latency will be predictive of lower MoCA scores.  
**H₃**: Participants who received two or more potentially neuroprotective multimodal anesthetic agents will demonstrate a larger positive change in their P300 amplitude, measured as a pre- to postoperative change score in microvolts.  
**H₄**: Participants who received two or more potentially neuroprotective multimodal anesthetic agents will demonstrate a smaller degree of prolongation in their P300 latency relative to their baseline, measured as a pre- to postoperative change score in milliseconds. |

Figure 22

Research Design for the Perioperative Brain Health Prospective Observational Trial

| O₁ | X | O₂ | O₃ |
| WAVi P300 | Anesthesia & Surgery | WAVi P300 Mini-Cog© CAM | WAVi P300 MoCA Mini-Cog© CAM |

Key:

O = observation  
X = intervention

Note: Mini-Cog© and CAM were used for the identification of POD
The “Perioperative Brian Health” – PID 22988, database is being created as part of an ongoing interdisciplinary perioperative brain health study with multiple research aims that are separate from this study. The database currently contains perioperative neurocognitive assessment records for 20 participants. Not all participants’ records in the database met the eligibility criteria for this study. The “test” or intervention refers to participants’ scheduled elective surgery and anesthetic. Preoperative baseline neurocognitive assessments were completed using the WAVi Medical™ software and hardware system and MoCA. Figure one depicts the WAVi Medical™ neurocognitive assessment platform. Appendix A presents the MoCA.

WAVi Medical™ scans were conducted and interpreted by trained research team members. WAVi Medical™ scans were performed as participants attempted an event-related response test. During the event-related response test, participants were asked to click a mouse when they heard a rare high-pitch tone within a series of low-pitch tones. The WAVi Medical™ system assessed participants’ neurocognitive activity during the auditory evoked potential testing and reported quantitative metrics of cognitive performance operationalized as time (in milliseconds) and voltage (in microvolts).

MoCA assessments were conducted and interpreted by trained research team members. One of the Perioperative Brian Health study’s (i.e., the data source for this study) investigators was MoCA-certified to administer and score MoCA assessments. This investigator trained research assistants to administer the MoCA v8.1 assessment based on Nasreddine’s (2017) MoCA v8.1 instructions for administering and scoring the MoCA. Research assistants successfully completed proctored simulated MoCA assessments on one another and at least two proctored clinical MoCA administrations prior to independently administering the MoCA
assessment to study participants. Nasreddine’s (2017) MoCA v8.1 standardized MoCA administration script was used for all MoCA assessments. The MoCA certified investigator scored all assessments.

Following surgery and anesthesia, participants underwent postoperative neurocognitive assessments using the WAViMed™ system, Mini-Cog®, and CAM. All assessments were conducted and interpreted by trained research assistants. The CAM Short Form was used by all evaluators. The Mini-Cog®, along with the WAVi P300 Assessment, was used as a standardized interview upon which to conduct the CAM evaluation as recommended by Inouye (2003). Appendix B presents the Mini-Cog® assessment. Appendix C presents the CAM Short Form. Appendix D presents the WAViMed™ system’s patent.

**Target & Accessible Populations**

The target population for this study was surgical patients over the age of 60 years presenting for elective, non-cardiac surgery and anesthesia. The accessible population was a convenience sample of surgical patients over the age of 60 years presenting to the VCU/VCUHS PACE clinic for preoperative evaluation and subsequently for surgery and anesthesia who underwent perioperative neurocognitive assessment while enrolled in the study “Perioperative Brain Health” – IRB HM20019839. VCU/VCUHS is a Level I trauma and regional referral center located in Richmond, Virginia that performs over 24,000 surgeries annually.

VCU is an urban public research university ranked among the top 100 research universities by the National Science Foundation and received over 335 million dollars in research funding in 2020 (Annual Report, 2020). This setting increased the likelihood that data source study’s findings would be generalizable to a wide variety of surgical procedures and across a large spectrum of patient conditions and comorbidities. Richmond, Virginia’s
population by race is: 48% Black or African American, 40% White or Caucasian, 6% Hispanic or Latino, 4% 2 or more races, 2% Asian, and <1% other (U.S. Census Bureau, 2019). The U.S. population is 60% White or Caucasian, 18% Hispanic or Latino, 13% Black or African American, 6% Asian, 2% having a combined two or more races, and <1% other (U.S. Census Bureau, 2019). Therefore, generalizability of the study results to some ethnic groups (e.g. Hispanic or Latino) in other regions of the United States may be limited by the research setting.

**Sampling Strategy**

For secondary data analysis, the sampling strategy is the method by which study participants are identified from the sampling frame (i.e., the available database) (Hulley et al., 2013). For this study, the VCU/VCUHS REDCap® database: “Perioperative Brain Health” – PID 22988 was the sampling frame. Available participants in this database underwent a variety of elective non-cardiac surgeries (e.g., orthopedic, urologic, oncologic, and general) and anesthesia at VCU/VCHU between November 2020 and April 2021 and participated in the study “Perioperative Brain Health” – IRB HM20019839. The number of participants in the sample was limited by the number of participants with complete data records that met this study’s eligibility criteria. Adequate data to meet study aims was expected as this study was not aimed at testing efficacy and similar EEG-based delirium studies analyzed data sets of between 12 and 23 participants. (e.g., Evans et al., 2017; Mulkey et al., 2019; Vacas et al., 2016).

The “Perioperative Brain Health” – IRB HM20019839 study employed a convenience sampling strategy. All initial screening, consent, and evaluation procedures took place in the VCU Health PACE clinic immediately after the potential study participant completed their scheduled preoperative anesthetic evaluation appointment. With the approval and collaboration of the Anesthesiologist Director of PACE, the investigators reviewed the PACE clinic schedule.
each day to identify potential study participants scheduled for their preoperative anesthesia assessment in the PACE clinic the following day. Immediately following the patient's PACE clinic visit, PACE clinic staff asked each potential study participant if they would like to speak with a member of the “Perioperative Brain Health” study team about participating in an observational research study. Potential study participants were informed about the study by members of the research team and asked if they would like to participate. If yes, informed consent was obtained, and initial observations were completed in a PACE clinic exam room.

**Eligibility Criteria**

Two eligibility criteria were used when identifying study participants from the VCU/VCUHS REDCap® database: “Perioperative Brain Health” – PID 22988 sampling frame. Eligibility criteria and their rationale for both this study and the data source study are listed in Table eight.

**Table 8**

*Eligibility Criteria and Rationale*

<table>
<thead>
<tr>
<th>Current proposed study</th>
<th>Criteria</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
<td>Sufficient data record to meet the aims of this study.</td>
<td>A subset of participants in the study data base did not have adequately complete data records for analysis due to a combination of factors including patient safety, patient satisfaction, and COVID-19 related assessment limitations.</td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
<td>EEG artifact that precludes high quality assessment data (i.e., less than 30/40 artifact free P300 waveforms)</td>
<td>Excessive EEG artifact may render erroneous P300 data. Therefore, records were excluded if less than 30/40 artifact free P300 waveforms were successfully captured during the four-minute oddball paradigm assessment.</td>
</tr>
<tr>
<td><strong>Data Source</strong></td>
<td>Scheduled for an on-site preoperative anesthesia evaluation at the VCU Preoperative Assessment Communication and</td>
<td>1) Brain function assessments were performed in the PACE clinic rather than the preoperative holding area so as to not delay the operating room on the day of surgery</td>
</tr>
</tbody>
</table>
Table 8 Continued

<table>
<thead>
<tr>
<th><strong>Inclusion</strong></th>
<th><strong>Exclusion</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Education (PACE) clinic prior to surgery</td>
<td>Participants with documented baseline cognitive impairments that exclude them from providing informed consent</td>
</tr>
<tr>
<td>2) WAVi EEG Brain scans require an in-person assessment and cannot be performed remotely.</td>
<td>Informed consent was required for this study and participants who are unable to provide informed consent due to a severe baseline cognitive impairment would not be able to perform the planned cognitive screening assessments.</td>
</tr>
<tr>
<td>Greater than 60 years of age</td>
<td>Self-reported inability to hear stimulus tone</td>
</tr>
<tr>
<td>1) The risk of an adult patient experiencing postoperative delirium (POD) increases with age</td>
<td>The WAVi auditory P300 tests assess the speed and power with which a patient's brain differentiates between a high pitched auditory tone and a low pitched auditory tone. Patients who were unable to hear these tones were not able to participate in the WAVi auditory P300 brain assessments.</td>
</tr>
<tr>
<td>2) The highest risk age group for POD is greater than 60 years of age.</td>
<td></td>
</tr>
<tr>
<td>Anticipated to be under general anesthesia for greater than 1 hour</td>
<td></td>
</tr>
<tr>
<td>Duration of anesthesia is associated with an increased risk of POD.</td>
<td></td>
</tr>
<tr>
<td>Scheduled for surgery below the neck</td>
<td>Positive COVID-19 test result within the previous 14 days documented in the patient’s health record</td>
</tr>
<tr>
<td>Per the WAVi Instruction Manual (Version 0.9.8.17) &quot;Do not use the WAVi headset on or near skin that is bruised or weakened due to either injury or the medical condition of the patient.&quot;</td>
<td>To mitigate the risk of transmitting COVID-19 from one participant to another, participants with a documented positive COVID-19 test result in their health record within the previous 14 days were not eligible to participate.</td>
</tr>
</tbody>
</table>

**Power Analysis**

Power analysis enables *a priori* determination of sample size which enhances statistical conclusion validity and reduces the risk of a Type II error (Polit & Beck, 2017). *A priori* power analysis was performed using the Daniel Soper Statistical Power Calculator version 4.0 (Soper, 2021). An effect size of 0.5 was anticipated given the frequency of POD noted in the literature.
For the first study aim, a sample of 15 participants was analyzed. With two predictor variables, each considered independently as they measure two separate constructs of neurocognition, an anticipated effect size of 0.5, and \( \alpha \) of 0.05, the \textit{a priori} power of this analysis was calculated to be 0.94.

For the second study aim, a sample of 10 participants was analyzed in this study. A doubly multivariate design using a repeated-measures multivariate analysis of variance (MANOVA) would be the ideal analysis for this aim. However, \textit{a priori} power analysis indicated that results were likely to be substantially underpowered. With three predictors (i.e., the DV, the two groups, and the pre- to postoperative repeated analysis), an anticipated \( r^2 = 0.5 \), \( \alpha = 0.05 \), and \( n = 10 \), power would only be 0.46.

The next best analysis for aim two would be a one-way MANOVA with pre- and postoperative scores transformed into a single difference score. However, with two predictors (i.e., the DV, and the two groups), an anticipated \( r^2 = 0.5 \), \( \alpha = 0.05 \), and \( n = 10 \), power would only improve to 0.61. A power of greater than 0.8 is desired to support statistical conclusion validity (Tabachnick and Fidell, 2013). For this reason, a pair of one-way ANOVA analyses were planned and conducted for the second study aim. With one response variable, an effect size of 0.5, and \( \alpha \) of 0.05, the \textit{a priori} power of this analysis was calculated to be 0.8.

**Data Management**

Electronic study data was stored on a secure password protected university issued laptop and backed up on a secure password protected university-based cloud storage server. REDCap\textsuperscript{®} was used to manage all data for this study. Hard copies of data generated during this study were securely stored in a locked file cabinet and only made accessible to research staff as needed.
REDCap® is a cloud-based research software platform designed for rapid data collection and secure data storage (Harris et al., 2009). REDCap® was specifically designed to provide researchers with an easy-to-use, customizable secure location for the collection, storage and dissemination of clinical data (Harris et al., 2009). All participants’ protected health information remained confidential. In addition to the study measures (i.e., WAVi Medical™ P300 and MoCA), the following demographic data were collected and recorded for each participant: American Society of Anesthesiology Classification Score, age, sex, ethnicity, surgical procedure, length of surgery, primary anesthetic, and the administration of adjunct the potentially neuroprotective multimodal anesthetic agents under investigation (i.e., magnesium, lidocaine, and ketamine). Study data were only made available to members of the research team and VCU’s institutional review board (IRB) upon request. Data that could potentially identify individual participants (e.g., name, birthdate, date of surgery, etc.) will not be published. REDCap®’s embedded statistical software was used to perform descriptive statistics of the data set. Study data was exported from REDCap® into the IBM® Statistical Package for the Social Sciences (SPSS) version 26.0 to perform multivariate statistical analyses.

**Variables & Measures**

The predictor variables for the first study aim were auditory P300 amplitude and auditory P300 latency. The measurement for P300 amplitude was microvolts. The measurement for P300 latency was milliseconds. Measurement data for the aforementioned variables were continuous, ratio level data. Continuous variables may take on any value of a given scale (Tabachnick & Fidell, 2013). The precision of measurement for continuous variables is limited by the measurement instrument as opposed to a scale itself (Tabachnick & Fidell, 2013). Ratio level
data is interval data (i.e., each value increment on the measurement scale is equally divided) that has a natural zero starting point (Tabachnick & Fidell, 2013).

The criterion variable for the first study aim was participants’ preoperative MoCA score. MoCA is scored on a scale of 0-30 points with a score of 30 representing a correct answer on each assessment item. The measurement for MoCA score is a whole integer between zero and 30. Data for this variable was continuous, ratio level data.

The dependent variables for the second study aim were participants’ pre- to postoperative P300 amplitude and P300 latency change scores. The measurement for P300 amplitude was microvolts. The measurement for P300 latency was milliseconds. The independent variable for the second study aim was whether or not the participant received two or more potentially neuroprotective multimodal anesthetic adjunct medications (i.e., lidocaine, magnesium, and/or ketamine) intraoperatively. The measurement for this variable was YES or NO. Data for this variable was categorical. Table nine categorizes the study variables.

Table 9
*Variables, Measurements, and Data Classification*

<table>
<thead>
<tr>
<th>Study Aim</th>
<th>Variable</th>
<th>Dependent (DV) vs Independent (IV)</th>
<th>Measurement</th>
<th>Data Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MoCA Score</td>
<td>DV</td>
<td>Whole Integer (0-30)</td>
<td>Continuous, Ratio</td>
</tr>
<tr>
<td></td>
<td>P300 Amplitude</td>
<td>IV</td>
<td>Microvolts</td>
<td>Continuous, Ratio</td>
</tr>
<tr>
<td></td>
<td>P300 Latency</td>
<td>IV</td>
<td>Milliseconds</td>
<td>Continuous, Ratio</td>
</tr>
<tr>
<td>2</td>
<td>P300 Amplitude Change Score</td>
<td>DV</td>
<td>Microvolts</td>
<td>Continuous, Ratio</td>
</tr>
<tr>
<td></td>
<td>P300 Latency Change Score</td>
<td>DV</td>
<td>Milliseconds</td>
<td>Continuous, Ratio</td>
</tr>
<tr>
<td></td>
<td>PNMMMAA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IV</td>
<td>YES / NO</td>
<td>Categorical</td>
</tr>
</tbody>
</table>

<sup>a</sup> potentially neuroprotective multimodal anesthetic adjuncts
Protection of Human Participants

Data for this study was secondary data collected from the VCU/VCUHS REDCap® database: “Perioperative Brain Health” – PID 22988. All participant’s protected health information was kept confidential in accordance with the Health Insurance Portability and Accountability ACT (HIPAA) of 1996 throughout this study. No personal identifiable patient information was collected for this study. This study did not require informed consent as it represented no more than minimal risk to the study patient. All participants whose records were utilized for this study previously gave informed consent to participate in the study “Perioperative Brain Health” – IRB HM20019839. The signed IRB approved consent forms for the study “Perioperative Brain Health” – IRB HM20019839 stated “In the future, identifiers might be removed from the information you provide in this study, and after that removal, the information could be used for other research studies by this study team or another researcher without asking you for additional consent.”

Data Cleaning

After data for this study was exported from REDCap®, variables were named and data was evaluated as described by Tabachnick and Fidell (2013) chapter four. First, accuracy of the recorded data was assessed. Next, the data set was evaluated for missing data and would have been reconciled by performing a value analysis to evaluate for magnitude and patterns of missing data. Not missing data was identified. Third, data fit was assessed for the assumptions of each multivariate statistical analysis. Fourth, data would have been transformed if necessary. No data required transformation. Finally, the data set was evaluated for outliers which would have been acknowledged and handled as indicated by accepted best statistical practices. No outliers were identified.
**Descriptive Statistics**

Descriptive statistics portray a study’s sample population and use this information to describe the reference population (Tabachnick and Fidell, 2013). This study generated descriptive statistics to depict the characteristics of a sample of older surgical patients presenting for surgery and anesthesia who participated in the study “Perioperative Brain Health” – IRB HM20019839 and met eligibility criteria for this study. The following descriptive statistics are reported in chapter five: 1) sample size, 2) age (range and mean), 3) sex (% female vs male), 4) ethnicity (% African American, Caucasian, Hispanic or Latino, 2 or more races, Asian, and other), 5) American Society of Anesthesiology Classification Score, 6) surgical procedure (nominal), 7) length of surgery (range and mean), 8) type of anesthetic (nominal), 9) duration of anesthetic, and 10) the administration of potentially neuroprotective multimodal anesthetic adjunct medications (categorical).

**Multivariate Statistics**

Regression was used in the evaluation of data for the first study aim to assess whether auditory P300 amplitude (in microvolts) or auditory P300 latency (in milliseconds) predicted participants’ MoCA scores. Regression was appropriate for this analysis as it aims to create a linear combination of independent variables that optimally predict a dependent variable and identify the relative contribution of each independent variable to the total variance explained by the model. Once collected, data were analyzed for the following eight assumptions prior to performing regression analysis (Laerd, 2021a):

1. The dependent variable was interval or ratio level data
2. There were two or more independent variables with continuous data
3. Independence of observations was present
4. Normality was present
5. There was a linear relationship between the two variables
6. Homoscedasticity was present
7. Multicollinearity was absent
8. There were no significant outliers

Assumptions one, two, and three were self-evident from the data set as displayed in tables nine and 10. Histograms were generated to assess normality. Scatterplots were generated to assess linearity, homoscedasticity, and outliers. A Pearson correlation matrix was generated to assess for multicollinearity. The results for assumption testing including histograms, scatterplots, and SPSS output are discussed and displayed in chapter five. Each variable was considered independently as they measure two separate constructs of neurocognition, namely cognitive resources (i.e., brain power) and cognitive efficiency (i.e., brain speed).

The ideal statistical analysis for the second study aim would have been a doubly multivariate design using a repeated-measures multivariate analysis of variance (MANOVA). This approach would enable the evaluation of multiple non-commensurate dependent variables (e.g., P300 latency and P300 amplitude which are measured on different scales: microvolts and milliseconds respectively) that are repeatedly measured (e.g., pre- and postoperatively) (Tabachnick and Fidell, 2013). This design enables singly multivariate evaluation of the between-subjects effect (i.e., those who received potentially neuroprotective multimodal anesthetic adjunct medications versus those who did not) and doubly multivariate evaluation of the within-subjects effects (i.e., pre- versus postoperative values of the dependent variables). This analysis would test for parallelism, flatness, and levels (Tabachnick and Fidell, 2013). Of these three, parallelism testing would be of the highest utility for this study to evaluate for a
difference in neurocognitive metrics between participants who received potentially neuroprotective anesthetics adjuncts and participants who did not. The sample size required for this analysis is set by the between-subjects effect according to the conditions for MANOVA. With the current sample size available in the data source study (i.e., postoperative assessment \( n=10 \)), results from this analysis were estimated to be substantially underpowered in the \textit{a priori} power analysis. For example, with three predictors (i.e., the DV, the two groups, and the pre- to postoperative repeated analysis), an anticipated \( r^2 = 0.5, \alpha = 0.05, \) and \( n = 10 \), power would only be 0.46. To support statistical conclusion validity, a power of greater than 0.8 is desired (Tabachnick and Fidell, 2013). For this reason, a doubly multivariate design using a repeated-measures MANOVA was not used for this study as this design uses one degree of freedom comparing pre- to postoperative scores and one degree of freedom for the two groups.

The second best statistical analysis for the second study aim would have been to conduct a one-way MANOVA by converting the pre- and postoperative scores into a single difference score. This would reduce the number of predictors by one and reduce the degrees of freedom used by one. However, with two predictors (i.e., the DV, and the two groups), an anticipated \( r^2 = 0.5, \alpha = 0.05, \) and \( n = 10 \), power would only improve to 0.61. For this reason, a one-way MANOVA of difference scores was not used for this study.

A pair of one-way ANOVA analyses were conducted for the second study aim to determine whether a difference exists in pre-and postoperative P300 amplitude (in microvolts) and P300 latency (in milliseconds) change scores between participants who received potentially neuroprotective multimodal anesthetic adjunct medications and those who did not. ANOVA is appropriate for this analysis because it aims to determine if a statistically significant difference exists between the means of two or more independent groups, minimizes the effect of the degrees
of freedom, and maximizes the power for a small sample (Tabachnick and Fidell, 2013). With one response variable, an effect size of 0.5, and $\alpha$ of 0.05, the a priori power of this analysis was calculated to be 0.8. After being collected, data was analyzed for the following six assumptions prior to performing an ANOVA (Laerd, 2021b):

1. The dependent variable was interval or ratio level data
2. The independent variable consisted of two or more independent, categorical groups
3. There was independence of observations
4. There were no significant outliers
5. The dependent variables were approximately normally distributed for each category of the independent variable
6. Homogeneity of variance was present

Assumptions one, two, and three were self-evident from the data set as displayed in tables nine and 10. Histograms were generated to assess normality. Scatterplots were generated to assess linearity, homogeneity of variance, and outliers. Chapter five includes a discussion of the results of assumption testing and displays figures of the histograms, scatterplots, and SPSS output generated in this process.

Assumptions & Limitations

The principal assumption in this study is that the WAVi Medical™ system provides valid and reliable assessment of P300 waveforms in response to an oddball paradigm as the device was not independently validated by the research team. This assumption is reasonable given: 1) previously reported utility of P300 evoked potentials as a neurocognitive assessment metric (Sur & Sinha, 2009; Parra et al., 2012; Yener, 2013, van Dinteren 2014; Grover et al., 2017; Clayton et al. 2020), 2) reported success using the WAVi Medical™ system for conducting P300 evoked
potential neurocognitive assessments in at least two recent publications (Grover et al., 2017; Clayton et al., 2020), and 3) similar ongoing neurocognition clinical studies are employing the WAVi Medical™ system (National Institutes of Health, 2018; Clinicaltrials.gov, 2018). Mulkey et al. (2019) accepted comparable assumptions as the first investigators to evaluate the potential utility of the Ceribell device (Ceribell, Inc., 2018), an FDA-cleared limited lead EEG device, for delirium identification and assessment among ICU patients.

One limitation of a retrospective secondary data study is that causality cannot be determined (Polit and Beck, 2017). As a proof-of-concept study, this study primarily sought to identify associations that may be useful in generating hypotheses to guide future research. Another potential limitation of a study that uses secondary data is that data could be inaccurate or incomplete (Hulley et al., 2013). Additionally, data may have been collected from an unideal population (e.g., unequal proportions of gender, age, or ethnicity) and important covariates may not have been identified and recorded (Hulley et al., 2013). A third potential limitation of this study is the relatively higher likelihood of a Type II error (i.e., failing to reject a false null hypothesis) given the relatively small postoperative assessment sample size available from the data source study. A more detailed discussion of limitations is presented in chapter six.

Chapter Summary

This study was important because the WAVi Medical™ system may one day enable anesthesia providers to: 1) rapidly perform a valid and reliable neurocognitive assessment that is more detailed, sensitive, and specific than questionnaire-based neurocognitive screening tools, 2) predict POD risk and stratify patients into risk categories, 3) detect mild cognitive impairments currently missed by brief cognitive screening tools (e.g., Mini-Cog©), and 4) objectively track the progression of postoperative cognitive changes over time. Specifically, this study
investigated the potential clinical utility of P300 AEP (i.e., amplitude and latency) obtainable with a POC EEG brain health assessment device. This contribution was significant because, pending further investigation, a device capable of rapidly and reliably predicting, identifying, and tracking perioperative neurocognitive disorders may enhance anesthesia providers’ ability to develop and evaluate the effectiveness of perioperative brain health protection protocols and clinical pathways in an effort to reduce the incidence and severity of POD in older surgical patients (Axley & Schenning, 2015).
Chapter 5: Results

Chapter Overview

The purpose of this study was to explore baseline and postoperative neurocognitive characteristics that may help to establish novel predictive and trend metrics for perioperative neurocognitive assessment in older surgical patients. In this study, relationships between P300 AEPs and MoCA scores were explored, and differences in pre- to postoperative P300 AEP change scores between participants who received two or more potentially neuroprotective multimodal anesthetic adjunct medications versus those who did not were evaluated. This study was important because neurobiomarkers obtainable with the POC EEG brain health assessment device, WAVi Medical™ (Boulder, CO), might one day provide anesthesia providers with a more detailed perioperative assessment of a patient’s brain, the primary target of anesthesia, than is currently available with questionnaire-based assessment tools (e.g., MoCA, Mini-Cog©, and CAM).

A non-experimental ex post facto secondary data analysis design was used to retrospectively: 1) compare participants’ baseline P300 AEPs to MoCA scores before surgery and anesthesia and 2) evaluate for group differences in pre- to postoperative P300 AEP change scores between participants who received two or more potentially neuroprotective multimodal anesthetic adjunct medications versus those who did not.

Chapter five offers a succinct presentation of the study’s results. Results are presented in a narrative format supplemented with figures and tables. The chapter begins with a description of
the variables and data cleaning process and is followed by a summary of the statistical findings for each of the two study aims.

Review of Data Acquisition

Following IRB approval from VCU, data records meeting this study’s criteria were extracted from the VCU/VCUHS REDCap® database: “Perioperative Brain Health” – PID 22988. As previously mentioned, data in this database was collected using a longitudinal, repeated measures design to conduct a prospective observational trial with a set of pretests and multi-observation post-tests. At the time of data extraction for the current study, the database contained 20 participant records. After the evaluation of each record for sufficient data to meet this study’s inclusion and exclusion criteria, the final sample size was $n = 15$ for the first study aim and $n = 10$ for the second study aim. Figure 23 illustrates the study’s exclusion criteria for both study aims.

**Figure 23**  
*Study Exclusion Flow Chart*
Data Preparation and Cleaning

Data was inspected for accuracy and missing values. No missing values were identified.

Data was coded using SPSS and assigned as either scale (i.e., continuous) or nominal (i.e., categorical) in SPSS for the purpose of analysis. Table 10 lists the study variables and their respective coding.

Table 10

Study Variables and Coding

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coding</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age in years</td>
<td>Scale / Continuous</td>
</tr>
<tr>
<td>Sex</td>
<td>1 = “Male”</td>
<td>Nominal / Categorical</td>
</tr>
<tr>
<td></td>
<td>2 = “Female”</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>1 = “African American”</td>
<td>Nominal / Categorical</td>
</tr>
<tr>
<td></td>
<td>2 = “Caucasian”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 = “Hispanic or Latino”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 = “Asian”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 = “2 or more races”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 = “Self-identify”</td>
<td></td>
</tr>
<tr>
<td>ASA Score</td>
<td>1 = “ASA I - A normal healthy patient”</td>
<td>Nominal / Categorical</td>
</tr>
<tr>
<td></td>
<td>2 = “ASA II - A patient with mild systemic disease”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 = “ASA III - A patient with severe systemic disease”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 = “ASA IV - A patient with severe systemic disease that is a constant threat to life”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 = “ASA V - A moribund patient who is not expected to survive without the operation”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 = “ASA VI - A declared brain-dead patient whose organs are being removed for donor purposes”</td>
<td></td>
</tr>
<tr>
<td>MoCA Score</td>
<td>Score 0-30</td>
<td>Scale / Continuous</td>
</tr>
<tr>
<td>P300 Amplitude</td>
<td>Amplitude in microvolts</td>
<td>Scale / Continuous</td>
</tr>
<tr>
<td>P300 Latency</td>
<td>Latency in milliseconds</td>
<td>Scale / Continuous</td>
</tr>
<tr>
<td>Primary Anesthetic</td>
<td>1 = “Sevoflurane”</td>
<td>Nominal / Categorical</td>
</tr>
<tr>
<td></td>
<td>2 = “Isoflurane”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 = “Desflurane”</td>
<td></td>
</tr>
</tbody>
</table>
Table 10 Continued

| Primary Anesthetic | 4 = “Propofol”  
5 = “Other”\(^a\) | Nominal / Categorical |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Anesthesia</td>
<td>Time in minutes</td>
<td>Scale / Continuous</td>
</tr>
</tbody>
</table>
| Surgical Procedure | 0 = “Spine”  
1 = “Shoulder Arthroplasty”  
2 = “Major Invasive Urology”  
3 = “Laparoscopic Intraabdominal” | Nominal / Categorical |
| Length of Surgery | Time in minutes | Scale / Continuous |
| PNMMMA Received (≥2) | 0 = “No”  
1 = “Yes” | Nominal / Categorical |
| P300 Amplitude Change Score | Pre- to postoperative amplitude change in microvolts | Scale / Continuous |
| P300 Amplitude Change Score | Pre- to postoperative latency change in milliseconds | Scale / Continuous |

\(^a\) No study participants were in this category

Descriptive Statistical Analysis

Descriptive analysis was completed using REDCap\(^®\)’s imbedded statistical software. The following descriptive statistics are presented in a narrative format supplemented with figures and tables: 1) sample size, 2) age (range and mean), 3) sex (% female vs male), 4) ethnicity (% African American and Caucasian), 5) American Society of Anesthesiology Classification Score, 6) surgical procedure (nominal), 7) length of surgery (range and mean), 8) type of anesthetic (nominal), 9) duration of anesthetic, and 10) the administration of PNMMMA agents (categorical).

For the first study aim, evaluate the ability of participants’ preoperative baseline P300 latency and P300 amplitude to predict participants’ cognitive function, the final sample size was 15. Participants’ age ranged from 61-82. The mean age was 72. Four participants identified as female (27%), and 11 participants identified as male (73%). Four participants identified as
African American (27%), and 11 participants identified as Caucasian (73%). Table 11 summarizes the descriptive statistics for the study aim one.

**Table 11**

*Descriptive Statistics – Aim 1*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Continuous: Mean (Min, Max)</th>
<th>Categorical: n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td><em>n = 15</em></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>72 (61, 82)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4 (27)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (73)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>4 (27)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>11 (73)</td>
<td></td>
</tr>
<tr>
<td>ASA Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>3 (20)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>10 (67)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>2 (13)</td>
<td></td>
</tr>
</tbody>
</table>

For study aim two, evaluate for group differences in pre- to postoperative P300 AEP change scores between participants who received two or more potentially neuroprotective multimodal anesthetic adjunct medications versus those who did not, the final sample size was 10. The sample size of group one (i.e., participants who did receive two or more PNMMA medications) was six. Group one participants’ age ranged from 66-79. The mean age was 73.2. Three participants identified as female (50%), and three participants identified as male (50%). Two participants identified as African American (33%), and four participants identified as Caucasian (67%). Two participants’ (33%) ASA was II, three participants’ (50%) ASA was III, and one participant’s (17%) ASA was IV. All participants in group one received a sevoflurane-based anesthetic. Group one’s duration of anesthesia ranged from 200-495 minutes. The mean duration of anesthesia for group one was 299 minutes. Two participants (33%) underwent
laparoscopic intra-abdominal surgery. Three participants (50%) underwent major invasive urologic surgery. One participant (17%) underwent shoulder arthroplasty. Group one participants’ length of surgery ranged from 150-428 minutes. The mean duration of surgery for group one was 253 minutes.

The sample size of group two (i.e., participants who did not receive two or more PNMMA medications) was four. Group two participants’ age ranged from 72-82. The mean age was 76.5. One participant identified as female (25%), and three participants identified as male (75%). All four participants identified as Caucasian (100%). One participant’s (25%) ASA was II and three participants’ (75%) ASA was III. One participant (25%) in group two received a propofol-based anesthetic, and three participants (75%) in group two received a sevoflurane-based anesthetic. Group two’s duration of anesthesia ranged from 97-293 minutes. The mean duration of anesthesia for group two was 218 minutes. Two participants (50%) underwent major orthopedic spine surgery. Two participants (50%) underwent shoulder arthroplasty. Group two participants’ length of surgery ranged from 69-214 minutes. The mean duration of surgery for group two was 167 minutes. Table 12 summarizes the descriptive statistics for the second study aim.

As previously noted, the target population for this study was surgical patients over the age of 60 years presenting for elective, non-cardiac surgery and anesthesia. The accessible population was a convenience sample of surgical patients over the age of 60 years presenting to the VCU/VCUHS PACE clinic for preoperative evaluation and subsequently for surgery and anesthesia who underwent perioperative neurocognitive assessment while enrolled in the study “Perioperative Brain Health” – IRB HM20019839. This setting increased the likelihood that study results would be generalizable to a wide variety of surgical procedures and across a large
### Table 12

*Descriptive Statistics – Aim 2*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PNMMA – Yes</td>
<td>PNMMA – No</td>
</tr>
<tr>
<td></td>
<td>Continuous: Mean (Min, Max)</td>
<td>Continuous: Mean (Min, Max)</td>
</tr>
<tr>
<td></td>
<td>Categorical: n (%)</td>
<td>Categorical: n (%)</td>
</tr>
<tr>
<td>Sample Size</td>
<td>n = 6</td>
<td>n= 4</td>
</tr>
<tr>
<td>Age</td>
<td>73.2 (66, 79)</td>
<td>76.5 (72, 82)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3 (50)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Male</td>
<td>3 (50)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>2 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Caucasian</td>
<td>4 (67)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>ASA Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2 (33)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>III</td>
<td>3 (50)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Primary Anesthetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>0</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>6 (100)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Length of Anesthesia (Minutes)</td>
<td>299 (200, 495)</td>
<td>218 (97, 293)</td>
</tr>
<tr>
<td>Surgical Procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>2 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Intraabdominal</td>
<td>3 (50)</td>
<td>0</td>
</tr>
<tr>
<td>Major Invasive Urology</td>
<td>1 (17)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Spine</td>
<td>0</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Shoulder Arthroplasty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of Surgery (Minutes)</td>
<td>253 (159, 428)</td>
<td>167 (69, 214)</td>
</tr>
</tbody>
</table>

Spectrum of patient conditions and comorbidities. Given the sample size for this study, a true representation of the diversity of the general population of older surgical patients is not realistically feasible. However, the sample population is reasonably diverse including participants from male and female gender, two ethnic groups, and ages ranging from 66-82.
Assumption Testing

Prior to performing multivariate statistical analysis, each variable was evaluated for the following assumptions:

Regression:

1. The dependent variable was interval or ratio level data
2. There were two or more independent variables with continuous data
3. Independence of observations was present
4. Normality was present
5. There was a linear relationship between the two variables
6. Homoscedasticity was present
7. Multicollinearity was absent
8. There were no significant outliers

Assumptions one, two, and three are self-evident from the data set as previously displayed in tables nine and ten. Histograms were generated to assess for normality (i.e., a normal distribution of the variables in a data set), skewness (i.e., symmetry of a data set’s distribution), and kurtosis (i.e., peakedness of a data set’s distribution) (Tabachnick and Fidell, 2013).

Skewness and kurtosis can be assessed both graphically (e.g., histogram with a curve overlay) and statistically. A graphed data set that is positively skewed has an increased number of data points on the left side of the histogram and a long right-sided tail on the curve overlay. A graphed data set that is negatively skewed has an increased number of data points on the right side of the histogram and a long left-sided tail on the curve overlay. Positive kurtosis refers to a tall, peaked distribution with short, thick tails on a histogram relative to a normal distribution, and negative kurtosis refers to a flattened distribution (Tabachnick and Fidell, 2013). Skewness
and kurtosis statistics can be converted to z-scores by dividing the statistic by its standard error with the acceptable range being a z-score of negative three to positive three (Tabachnick and Fidell, 2013).

Scatterplots were generated to assess for linearity (i.e., a straight-line forming association between two variables), homoscedasticity (i.e., one variable’s variance is identical across all values for another variable), and outliers (i.e., data points that significantly differ from the majority of other data points within a data set) (Tabachnick and Fidell, 2013). A Pearson correlation matrix of the independent variables was created to assess for multicollinearity (i.e., correlated independent variables) (Tabachnick and Fidell, 2013). A Pearson correlation of less than 0.8 is indicative of an acceptable absence of multicollinearity among variables (Tabachnick and Fidell, 2013).

For aim one, the DV was MoCA score and the IVs were P300 amplitude and latency. The distribution of the DV (i.e., MoCA Score) exhibited a negative skewness (i.e., skewed left) of -1.31 (standard error 0.58) and positive kurtosis of 1.05 (standard error 1.12). The distribution of the IV amplitude exhibited a slight positive skewness (i.e. skewed right) of 0.55 (standard error 0.58) and slight positive kurtosis of 0.32 (standard error 1.12). The distribution of the IV latency exhibited a slight positive skewness (i.e., skewed right) of 0.15 (standard error 0.58) and slight positive kurtosis of 0.36 (standard error 1.12). Figures 24, 25, and 26 display the histograms with a curve overlay generated in SPSS for aim one. Figure 27 displays the results of statistical analysis for skewness and kurtosis of the aim one variables.

The MoCA-amplitude scatterplot exhibited a weak negative relationship. Homogeneity of variance was present and appeared relatively consistent, and no extreme outliers were noted. Figure 28 displays the MoCA-amplitude scatterplot. The MoCA-latency scatterplot exhibited a
weak positive relationship. Homogeneity of variance was present and appeared relatively consistent on the MoCA-latency scatterplot. No extreme outliers were noted.

Figure 25

Histogram of the Distribution of the Aim One IV, Amplitude
Figure 26

Histogram of the Distribution of the Aim One IV, Latency

Figure 27

SPSS Output: Skewness and Kurtosis of the Aim One Variables

<table>
<thead>
<tr>
<th>Descriptive Statistics</th>
<th>N Statistic</th>
<th>Skewness Statistic</th>
<th>Std. Error</th>
<th>Kurtosis Statistic</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoCA Score</td>
<td>15</td>
<td>-1.312</td>
<td>.580</td>
<td>1.053</td>
<td>1.121</td>
</tr>
<tr>
<td>Amplitude (Pre-op)</td>
<td>15</td>
<td>.545</td>
<td>.580</td>
<td>.319</td>
<td>1.121</td>
</tr>
<tr>
<td>Latency (Pre-op)</td>
<td>15</td>
<td>.147</td>
<td>.580</td>
<td>.359</td>
<td>1.121</td>
</tr>
<tr>
<td>Valid N (listwise)</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 29 displays the MoCA-latency scatterplot. A Pearson correlation matrix was generated to assess for multicollinearity between the two independent variables (i.e., amplitude and latency). The Pearson correlation was calculated to be $r = -0.111, n = 15$, and the relationship was not significant $p = 0.695$. Multicollinearity was not present. Figure 30 displays the SPSS output for the correlation matrix.
Figure 28

Scatterplot of the Distribution of the Aim One IV, Amplitude and DV, MoCA Score

Figure 29

Scatterplot of the Distribution of the Aim One IV, Latency and DV, MoCA Score
Figure 30

SPSS Output: Collinearity Statistics of the Aim One Variables

<table>
<thead>
<tr>
<th></th>
<th>Amplitude (Pre-op)</th>
<th>Latency (Pre-op)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude (Pre-op)</td>
<td>Pearson Correlation</td>
<td>-.111</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.695</td>
</tr>
<tr>
<td>N</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Latency (Pre-op)</td>
<td>Pearson Correlation</td>
<td>-.111</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.695</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

ANOVA:

1. The dependent variable was interval or ratio level data
2. The independent variable consisted of two or more independent, categorical groups
3. There was independence of observations
4. There were no significant outliers
5. The dependent variables were approximately normally distributed for each category of the independent variable
6. Homogeneity of variance was present

Assumptions one, two, and three for aim two were also self-evident from the data set previously displayed in tables nine and 10. Histograms were generated to assess for normality (i.e., a normal distribution of the variables in a data set), skewness (i.e., symmetry of a data set’s distribution), and kurtosis (i.e., peakedness of a data set’s distribution) (Tabachnick and Fidell, 2013).

As previously noted for aim one, skewness and kurtosis may be assessed graphically (e.g., histogram with a curve overlay), statistically, or by a combination of the two. A positively skewed data set presents as an increased number of data points on the left side of the histogram and a long right-sided tail on the curve overlay. A negatively skewed data set presents as an
increased number of data points on the right side of the histogram and a long left-sided tail on the curve overlay. Positive kurtosis presents as a tall, peaked distribution with short, thick tails on a histogram, whereas negative kurtosis presents as a flattened curve relative to a normal distribution (Tabachnick and Fidell, 2013). The calculated statistics for skewness and kurtosis can be converted to z-scores by dividing the statistic by its standard error. The generally acceptable range for these values is a z-score between negative and positive three (Tabachnick and Fidell, 2013).

Scatterplots were generated to assess for linearity (i.e., a straight-line forming association between two variables), homoscedasticity (i.e., one variable’s variance is identical across all values for another variable), and outliers (i.e., data points that significantly differ from the majority of other data points within a data set) (Tabachnick and Fidell, 2013). For aim two, the DVs were P300 amplitude and latency change scores and the IV was whether or not (i.e., Yes / No) participants received two or more PNMMA adjunct medications.

The distribution of the DV P300 amplitude change score exhibited a slight positive skewness (i.e., skewed right) of 0.15 (standard error 0.69) and negative kurtosis of -2.189 (standard error 1.33). The distribution of the DV P300 latency change score exhibited a slight positive skewness (i.e., skewed right) of 0.05 (standard error 0.69) and slight negative kurtosis of -0.55 (standard error 1.33). The distribution of the IV PNMMA (Yes / No) exhibited a slight negative skewness (i.e. skewed left) of -0.48 (standard error 0.69) and negative kurtosis of -2.28 (standard error 1.34). Figures 31, 32, and 33 display the histograms with a normal curve overlay generated for aim two. Figure 34 displays the results of statistical analysis for skewness and kurtosis of the aim two variables.
Figure 31

Histogram of the Distribution of the Aim Two DV, Amplitude Change Score

Figure 32

Histogram of the Distribution of the Aim Two DV, Latency Change Score
Figure 33

*Histogram of the Distribution of the Aim Two IV, PNMMA (Yes / No)*

![Histogram of PNMMA](image)

Figure 34

*SPSS Output: Skewness and Kurtosis of the Aim Two Variables*

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Skewness Statistic</th>
<th>Skewness Std. Error</th>
<th>Kurtosis Statistic</th>
<th>Kurtosis Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPCHANGE</td>
<td>10</td>
<td>.154</td>
<td>.687</td>
<td>-2.189</td>
<td>1.334</td>
</tr>
<tr>
<td>LATCHANGE</td>
<td>10</td>
<td>.047</td>
<td>.687</td>
<td>-.548</td>
<td>1.334</td>
</tr>
<tr>
<td>PNMMA</td>
<td>10</td>
<td>-.484</td>
<td>.687</td>
<td>-2.277</td>
<td>1.334</td>
</tr>
<tr>
<td>Valid N (listwise)</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The PNMMA-amplitude boxplot displayed in Figure 35 exhibited a positive association between receiving PNMMA (Yes / No) and amplitude change scores. The PNMMA-latency boxplot displayed in Figure 36 exhibited little to no association between receiving PNMMA
Figure 35

Boxplot of the Aim Two DV, Amplitude Change Score and IV, PNMMA (Yes / No)

Figure 36

Boxplot of the Aim Two DV, Latency Change Score and IV, PNMMA (Yes / No)

(Yes / No) and latency change scores. Homogeneity of variance was present and appeared relatively consistent, and no extreme outliers were noted for these boxplots.
Statistical Analysis

The first study aim was to evaluate the ability of participants’ preoperative baseline P300 latency (i.e., brain speed) and P300 amplitude (i.e., brain power) to predict participants’ cognitive function. This study used regression to understand whether auditory P300 amplitude (in microvolts) and auditory P300 latency (in milliseconds) predict cognitive function among older surgical patients as assessed by MoCA. Each variable was considered independently as they measure two separate constructs of neurocognition, namely cognitive resources (i.e., brain power) and cognitive efficiency (i.e., brain speed).

Hypothesis one (H₁) assessed for a relationship between participants’ P300 amplitude and MoCA scores.

Hypothesis #1: Lower P300 amplitude will be predictive of lower MoCA scores.

H₁ was tested using linear regression. A simple linear regression was calculated to predict participants’ MoCA scores based on their P300 amplitude. The regression equation was not significant ($F(1,13) = 0.021, p > 0.05$) with an $r^2$ of 0.002. In this sample, P300 amplitude was not a significant predictor of MoCA score. Figures 37 and 38 show the model summary and coefficients for the analysis of H₁ respectively.

Figure 37

SPSS Output: Model Summary for Analysis of H₁

<table>
<thead>
<tr>
<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Adjusted R Square</th>
<th>Std. Error of the Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.040$^a$</td>
<td>.002</td>
<td>-.075</td>
<td>3.987</td>
</tr>
</tbody>
</table>

a. Predictors: (Constant), Amplitude (Pre-op)
Hypothesis two (H₂) assessed for a relationship between participants P300 latency and MoCA scores.

Hypothesis #2: Increased P300 latency will be predictive of lower MoCA scores. H₂ was tested using linear regression. A simple linear regression was calculated to predict participants’ MoCA scores based on their P300 latency. The regression equation was not significant ($F(1,13) = 0.052, p > 0.05$) with an $r^2$ of 0.004. In this sample, P300 latency was not a significant predictor of MoCA score. Figures 39 and 40 show the model summary and coefficients for the analysis of H₂ respectively.

**Figure 39**

*SPSS Output: Model Summary for Analysis of H₂*
The second study aim was to evaluate for group differences in pre- to postoperative P300 AEP change scores (i.e., amplitude (in microvolts) and latency (in milliseconds)) between participants who received two or more PNMMA medications (i.e., magnesium, lidocaine, and/or ketamine) versus those who did not.

Hypothesis three (H₃) assessed for a difference in P300 amplitude between participants who received two or more PNMMA medications versus those who did not.

Hypothesis #3: Participants who received two or more potentially neuroprotective multimodal anesthetic agents will demonstrate a larger positive change in their P300 amplitude, measured as a pre- to postoperative change score in microvolts.

A one-way ANOVA was computed to determine if participants who received two or more PNMMA agents demonstrated a larger positive change in their P300 amplitude than participants who did not receive these medications intraoperatively.

As seen in Figure 41, participants who did not receive two or more PNMMA medications had a mean reduction in their P300 amplitude (-3.5). However, participants who did receive two or more PNMMA medications had a mean increase in their P300 amplitude (4.3). These findings supported study aim two, hypothesis three.
As seen in Figure 42, in this sample, a significant difference was identified between the two groups \((F(1,8) = 12.093, p < 0.05)\).

**Figure 42**

**SPSS Output: ANOVA for Analysis of H₃**

<table>
<thead>
<tr>
<th></th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Between Groups</strong></td>
<td>145.393</td>
<td>1</td>
<td>145.393</td>
<td>12.093</td>
<td>.008</td>
</tr>
<tr>
<td><strong>Within Groups</strong></td>
<td>96.183</td>
<td>8</td>
<td>12.023</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>241.576</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Post hoc analysis revealed that participants who received two or more PNMMA medications demonstrated a larger positive postoperative change in their P300 amplitude \((M = 4.33, sd = 4.29, 95\% CI = [-0.17, 8.83])\) than participants who did not \((M = -3.45, sd = 1.19, 95\% CI = [-5.34, -1.56])\).

Hypothesis four \((H₄)\) assessed for a difference in P300 latency between participants who received two or more PNMMA medications versus those who did not.

Hypothesis #4: Participants who received two or more potentially neuroprotective multimodal anesthetic agents will demonstrate a smaller degree of prolongation in their
P300 latency relative to their baseline, measured as a pre- to postoperative change score in milliseconds.

A one-way ANOVA was computed to determine if participants who received two or more PNMMA agents demonstrated a smaller degree of prolongation in their P300 latency than participants who did not receive these medications intraoperatively. No significant difference was identified \( (F(1, 8) = 0.245, p > 0.05) \). Participants’ P300 latency change scores did not differ significantly between the two groups. Participants who received two or more PNMMA agents had a mean change score of 14.76 milliseconds \( (sd = 76.01, 95\% \text{ CI} = [-65.10, 94.43]) \).

Participants who did not receive two or more PNMMA agents had a mean change score of -9 milliseconds \( (sd = 70.53, 95\% \text{ CI} = [-121.23, 103.23]) \). Figures 43 and 44 show the descriptives and ANOVA for the analysis of H₄.

**Figure 43**

**SPSS Output: Descriptives for Analysis of H₄**

<table>
<thead>
<tr>
<th>Lat. Change Score (Pre–to–Post op)</th>
<th>Descriptives</th>
<th>95% Confidence Interval for Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>-9.00</td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>14.67</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>5.20</td>
</tr>
</tbody>
</table>

**Post Hoc Power Analysis**

*Post hoc* power analysis was performed using the Daniel Soper Statistical Power Calculator version 4.0 (Soper, 2021). In the *post hoc* power analysis, the power of the first study aim was calculated to be very low at 0.05 for each predictor \( (n = 15, 2 \text{ predictors (considered independently as they measure two separate constructs of neurocognition)) calculated effect size of } 0.002 \text{ (amplitude) and } 0.004 \text{ (latency), and } \alpha \text{ of } 0.05) \). This result was lower than anticipated
based on the *a priori* power analysis and indicates a 5% chance of detecting an effect if one exists and a 95% chance of a Type II error, a false acceptance of the null hypothesis.

**Figure 44**

*SPSS Output: ANOVA for Analysis of H₄*

<table>
<thead>
<tr>
<th>Lat. Change Score (Pre–to–Post op)</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>1344.267</td>
<td>1</td>
<td>1344.267</td>
<td>.245</td>
<td>.634</td>
</tr>
<tr>
<td>Within Groups</td>
<td>43809.333</td>
<td>8</td>
<td>5476.167</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>45153.600</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For second study aim, hypothesis three, the *post hoc* power was calculated to be acceptable at 0.94 (*n* = 10, 1 response, calculated effect size of 0.6, and *α* of 0.05). This result was slightly higher than anticipated based on the *a priori* power analysis and indicates an 94% chance of detecting an effect if one exists and a 16% chance of a Type II error, false acceptance of the null hypothesis. For second study aim, hypothesis four, the *post hoc* power was calculated to be very low at 0.08 (*n* = 10, 1 response, calculated effect size of 0.03, and *α* of 0.05). This result was lower than anticipated based on the *a priori* power analysis and indicates an 8% chance of detecting an effect if one exists and a 92% chance of a Type II error, false acceptance of the null hypothesis.

**Chapter Summary**

Chapter five presented the results of this study’s statistical analyses to evaluate the ability of participants’ preoperative baseline P300 latency and amplitude to predict participants’ MoCA scores and assess for group differences in pre- to postoperative P300 AEP change scores between participants who received two or more PNMMA medications versus those who did not. Linear
regression was used to analyze the relationship between participants’ preoperative baseline P300 latency and amplitude and MoCA scores. No significant relationship was identified between either P300 latency or amplitude and MoCA scores. ANOVA was used to evaluate for differences in pre- to postoperative P300 AEP change scores between participants who received two or more PNMMMA medications and those who did not. A statistically significant postoperative positive change in P300 amplitude was identified in participants who received two or more PNMMMA medications (e.g., lidocaine, ketamine, magnesium) versus those who did not. No significant postoperative change in P300 latency was identified in participants who received two or more PNMMMA medications (e.g., lidocaine, ketamine, magnesium) versus those who did not. Chapter six discusses potential clinical implications of these findings, study limitations, and recommendations for future research.
Chapter 6: Conclusions and Recommendations

Chapter Overview

Chapter six presents a study summary and the important conclusions drawn from the data presented in chapter five. The potential clinical implications for anesthesia practice are discussed. The chapter concludes with recommendations for future research.

The Problem

The perioperative brain health of older surgical patients is a public health and research priority (American Society of Anesthesiologists, 2019). POD is a risk factor for long-term neurocognitive decline, and the rate of decline is associated with POD severity (Vasunilashorn et al., 2018). Baseline cognitive function is a strong, independent predictor for POD (Culley et al., 2017). The International Perioperative Neurotoxicity Working Group recommends preoperative baseline neurocognitive assessment for older surgical patients (Berger, et al., 2018). Cognitive screening tools trialed in anesthesia are not routinely incorporated into clinical practice related to validity, reliability, or practicality considerations (Berger, et al., 2018). The ideal perioperative neurocognitive assessment would be rapid, easily-administrable, valid, reliable, automatically scored, void of language, cultural, and education bias and cost-efficient (Axley & Schenning, 2015). No such assessment has been identified to date.

Anesthesia providers routinely assess multiple organ systems (e.g., cardiovascular—auscultation of heart sounds, METs; respiratory—auscultation of lung sounds; laboratory values—hemoglobin/hematocrit, glucose, electrolytes, hepatic enzymes). However, the brain, anesthesia’s primary target, is rarely assessed beyond orientation to person, place, time and task.
Crosby et al. (2011) lamented this problem:

…that we currently make no effort to identify [older patients with a vulnerable brain state] preoperatively is an embarrassing state of affairs considering that… perioperative cognitive morbidity in the elderly is so common and costly (p. 1267).

One major barrier to rigorous and routine perioperative neurocognitive evaluation is that no easily-administrable, rapid, reliable, highly sensitive and specific assessment of an individual’s cognitive resources and efficiency is currently available.

A POC EEG device capable of rapidly performing easily-administrable, reliable, sensitive, and specific neurocognitive assessments at the bedside might enable anesthesia providers to better assess baseline neurocognitive function in older surgical patients prior to surgery and anesthesia. Objective assessments derived from a POC EEG-based neurocognitive assessment device may detect neurocognitive baseline changes as well as postoperative changes (e.g., mild or even subsyndromal cognitive impairments) that are currently missed in a subset of patients by clinically utilized cognitive assessment tools (e.g., A&O x4).

**Study Purpose, Research Questions, and Hypotheses**

As a proof-of-concept study, this research primarily sought to explore associations and generate hypotheses to guide future research. Specifically, the purpose of the study was to explore potential neurobiomarkers derived from EEG-based P300 auditory evoked potentials (AEPs) that may serve as both predictive and trend metrics of perioperative neurocognitive function in older surgical patients. Such neurobiomarkers might facilitate a more rigorous perioperative assessment of a patient’s brain state than do questionnaire-based assessment tools (e.g., What is your name?, Where are you right now?, What is today’s date?, Do you know why you are here?). In this study, relationships between P300 AEPs and MoCA scores were explored.
and differences in pre- to postoperative P300 AEP change scores between participants who received two or more PNMMa adjunct medications versus those who did not were evaluated. Pending further investigation, EEG-based neurobiomarkers may assist the development of perioperative brain health protection protocols that reduce the incidence and/or severity of perioperative neurocognitive disorders in older surgical patients. **Review of Theory**

Donabedian’s Theoretical Model for Evaluating the Quality of Medical Care guided the design and implementation of this study. Donabedian’s framework is the most commonly used theoretical framework for evaluating the quality of healthcare services (Ayanian and Markel, 2016). According to Donabedian, three concepts (i.e., structure, process, and outcome) are the guiding principles for quality improvement. Donabedian’s model was appropriate for this study because the model is descriptive, explanatory, accurate, practical, simple, consistent, and acute in identifying links between practice processes and patient outcomes in the perioperative setting (Birkmeyer et al., 2004; Centurion et al., 2018; Hannan et al., 2001; Moore et al., 2015; Rose et al., 2019; Tsai et al., 2013). **Review of the Methodology**

The study employed a non-experimental *ex post facto* secondary data analysis design. This design was used to retrospectively compare participants’ baseline P300 AEPs to MoCA scores before surgery and anesthesia and to evaluate for group differences in pre- to postoperative P300 AEP change scores between participants who received two or more PNMMa medications versus those who did not. This study’s research question was: Could P300 AEPs obtained using the WAVi Medical™ system potentially enhance perioperative brain health
assessment and provide neurobiomarkers that aid in the development of perioperative brain health protection protocols for older surgical patients?

Specific Aim #1: Evaluate the ability of participants’ preoperative baseline P300 latency (i.e., brain speed) and P300 amplitude (i.e., brain power) to predict participants’ cognitive function. This study used regression to understand whether auditory P300 amplitude (in microvolts) and auditory P300 latency (in milliseconds) predict cognitive function among older surgical patients as assessed by MoCA. Each variable was considered independently as they measure two separate constructs of neurocognition, namely cognitive resources (i.e., brain power) and cognitive efficiency (i.e., brain speed).

Hypothesis #1: Lower P300 amplitude will be predictive of lower MoCA scores.

Hypothesis #2: Higher P300 latency will be predictive of lower MoCA scores.

Specific Aim #2: Evaluate for group differences in pre- to postoperative P300 AEP change scores (i.e., amplitude (in microvolts) and latency (in milliseconds)) between participants who received two or more potentially neuroprotective multimodal anesthetic adjunct medications (i.e., magnesium, lidocaine, and/or ketamine) versus those who did not.

Hypothesis #3: Participants who received two or more potentially neuroprotective multimodal anesthetic agents will demonstrate a larger positive change in their P300 amplitude, measured as a pre- to postoperative change score in microvolts.

Hypothesis #4: Participants who received two or more potentially neuroprotective multimodal anesthetic agents will demonstrate a smaller degree of prolongation in their P300 latency relative to their baseline, measured as a pre- to postoperative change score in milliseconds.
Regression was completed to evaluate data for study aim #1 to assess whether auditory P300 amplitude (in microvolts) and auditory P300 latency (in milliseconds) predicted participants’ MoCA scores. A pair of one-way ANOVA analyses were completed for study aim #2 to determine whether a difference existed in pre-and postoperative P300 amplitude (in microvolts) and P300 latency (in milliseconds) change scores between participants who received two or more PNMMA medications and those who did not.

**Synopsis of Major Findings**

For study aim one, regression was employed to evaluate whether auditory P300 amplitude or latency were predictive of MoCA scores.

**H₁**: Lower P300 amplitude will be predictive of lower MoCA scores.

The regression equation was not significant \( (F(1,13) = 0.021, p > 0.05) \) with an \( r^2 \) of 0.002. P300 amplitude was not a significant predictor of MoCA score in this sample.

**H₂**: Increased P300 latency will be predictive of lower MoCA scores.

The regression equation was not significant \( (F(1,13) = 0.052, p > 0.05) \) with an \( r^2 \) of 0.004. P300 latency was not a significant predictor for MoCA score in this sample.

For study aim two, ANOVA was employed to evaluate for group differences in pre- to postoperative P300 AEP change scores between participants who received two or more PNMMA medications and participants who did not.

**H₃**: Participants who received two or more potentially neuroprotective multimodal anesthetic agents will demonstrate a larger positive change in their P300 amplitude, measured as a pre- to postoperative change score in microvolts.

The analysis identified a significant difference between the two groups \( (F(1,8) = 12.093, p < 0.05) \). *Post hoc* analysis revealed that participants who received two or more PNMMA
medications demonstrated a larger positive postoperative change in their P300 amplitude ($M = 4.33$, $sd = 4.29$, 95% CI = [-0.17, 8.83]) than participants who did not ($M = -3.45$, $sd = 1.19$, 95% CI = [-5.34, -1.56]).

**H₄:** Participants who received two or more potentially neuroprotective multimodal anesthetic agents will demonstrate a smaller degree of prolongation in their P300 latency relative to their baseline, measured as a pre- to postoperative change score in milliseconds.

No significant difference was identified in participants’ P300 latency change scores between the two groups ($F(1, 8) = 0.245$, $p > 0.05$). Participants who received two or more PNMMA agents had a mean change score of 14.76 ($sd = 76.01$, 95% CI = [-65.10, 94.43]). Participants who did not receive two or more PNMMA agents had a mean change score of -9 ($sd = 70.53$, 95% CI = -121.23, 103.23]).

**Findings Related to the Literature**

This study found no association between participants’ P300 AEPs and MoCA scores. However, the sample population for this study consisted of four participants that identified as African American (27%) and 11 that identified as Caucasian (73%). Rossetti et al. (2017) identified that several components of the MoCA and previously established cut-off points for cognitive impairment are not well suited for African Americans. In a sample of over 1,000 community-dwelling African Americans with an average age of 49 years and no subjective cognitive complaints, the mean MoCA score was 22 (Rossetti et al., 2017). In this Rossetti et al.’s study, 72% of participants were unable to complete the cube drawing task, 66% of participants recalled fewer than 4/5 delayed free recall words, 63% were unable to complete the sentence repetition task, and 45% failed the abstraction portion of the assessment (Rossetti et al.,
These factors all present challenges for the use of MoCA as a routine clinical preoperative neurocognitive screening tool as MoCA may underestimate neurocognitive function in African American patients (i.e., MoCA scores may be lower for African Americans than for Caucasians with an equivalent level of cognitive function). Future research may consider evaluating the relationship between P300 AEPs and MoCA scores while controlling for the impact of potential ethnic and/or education biases on MoCA scores. It is also possible that MoCA provides different information regarding a patient’s baseline neurocognitive state and ultimate risk for postoperative neurocognitive changes (e.g., POD) than do P300 AEPs.

This study also evaluated group differences in pre- to postoperative P300 AEP change scores between participants who received two or more PNMMA medications and participants who did not. Lidocaine, ketamine, and magnesium are each reported to potentially reduce the risk of postoperative cognitive impairment (Bhudia et al., 2007; Mack et al., 2009; Chen et al., 2015; and Hovaguimian et al., 2018). Of particular interest, is the possible synergistic effect of these potentially neuroprotective anesthetic adjunct medications. Mendonca et al. (2020) reported a positive synergistic effect using a combination of lidocaine and magnesium for perioperative pain management. Fang et al. (2020) reported that combining lidocaine with ketamine “may be beneficial in shortening the onset of anesthesia, promoting postoperative waking…and [reducing the] incidence of adverse reactions” compared to administering ketamine alone (p. 1). It is possible that similar synergistic neuroprotective effects exist when combining two or more PNMMA for older surgical patients.

While the hypothesized differences in amplitude were supported ($H_3$), the differences in latency ($H_4$) were not. This finding eludes to, but does not confirm, the possibility that a synergistic neuroprotective effect could exist in older surgical patients receiving these
medications. Of interest, the impact of sub-anesthetic doses of ketamine administered as a sole agent have been previously determined to reduce auditory evoked P300 amplitude without an impact on latency (Schwertner, et al., 2018). However, no studies that evaluated the impact of ketamine, lidocaine, and/or magnesium on pre- to postoperative P300 AEP change scores in the perioperative setting were identified in the literature. Future studies with larger sample sizes, higher statistical power, and the inclusion of covariate analysis are needed to investigate the potential neuroprotective effects of these medications and the potential utility of P300 AEPs as perioperative neurophysiologic biomarkers for trending cognitive function in the clinical setting.

Limitations

This study has limitations related to design, variable measures, and statistical analysis. These limitations may impact study findings and pose threats to the validity of study results. Study limitations are presented and discussed in this section.

Selection bias poses a threat to the internal validity of this study. Selection bias results from preexisting between-group differences when study participants are not randomized into groups (Polit and Beck, 2017). Preexisting group differences (i.e., potential covariate factors), other than the independent variable(s) may have confounding influence on the dependent variable(s) (Polit and Beck, 2017). In the absence of covariate analysis, internal validity is threatened (Polit and Beck, 2017).

For study aim 2, participants were assigned to one of two groups based on whether or not the participants received PNMMA medications as displayed by Table 12 in chapter five. One notable difference between these two groups was gender. In group one, 50% were male and 50% were female. In group two, 75% were male, and 25% were female. Based on the limited number of studies available, P300 amplitude may be impacted by gender (Melynyte et al., 2018). In a
recent systematic review, 50% of the studies reviewed by the authors demonstrated a higher amplitude on average for females versus males, purportedly resulting from anatomical and hormonal differences (Melynyte et al., 2018). The authors recommend that gender be considered as a potential covariate and note that additional studies and meta-analysis are needed to better determine the strength of association between P300 AEPs and gender (Melynyte et al., 2018).

If a significant gender-associated difference does exist and is not controlled for as a covariate in future studies, an identified between-groups difference in those who receive an intervention (e.g., neuroprotective medication) and those who do not could be misinterpreted. Due to the small, fixed sample size available for this retrospective exploratory secondary data analysis, covariates were not incorporated into the analysis. Additional covariates that may be considered in future studies include: age, length of anesthesia, pain, and the participants’ emotional state at the time of assessment. Future studies with larger sample sizes will benefit from evaluating covariates to improve internal validity.

Instrumentation effect poses a threat to the internal validity of this study. Instrumentation effect refers to a change in the assessment tool or methodology between two data collection points (Polit and Beck, 2017). Even if the same instrument is used for repeated assessments, instrumentation effect can bias study results if an assessment tool were more/less accurate on a follow-up assessment relative to the initial assessment (Polit and Beck, 2017). As previously mentioned, the principal assumption for this study was that the WAVi Medical™ system provides valid and reliable assessment of P300 AEPs as the device was not independently validated by the data source study’s research team. This assumption was considered reasonable given the reported: 1) utility of P300 AEPs as a neurocognitive assessment metric (Sur & Sinha, 2009; Parra et al., 2012; Yener, 2013, van Dinteren 2014; Grover et al., 2017; Clayton et al.
success using the WAVi Medical™ system for conducting P300 AEPs in at least two recent publications (Grover et al., 2017; Clayton et al., 2020), and 3) ongoing neurocognition clinical studies employing the WAVi Medical™ system (National Institutes of Health, 2018; Clinicaltrials.gov, 2018). However, without independent validation of the instrument or documented validation studies in the literature, one cannot be absolutely certain of a device’s test-retest reliability. Prior to future studies, independent validation of the test-retest reliability of the WAVi Medical™ system would reduce the potential for instrumentation effect and strengthen the internal validity of future studies utilizing this device.

Low statistical power poses a threat to the statistical conclusion validity of this study. At best, regression-based analyses are used to identify relationships between variables (Tabachnick and Fidell, 2013). As previously noted, no relationship was identified between preoperative P300 amplitude and MoCA scores (H1) nor between preoperative P300 latency and MoCA scores (H2). Hypothesized differences in pre- to postoperative amplitude change scores were supported (H3), but the hypothesized differences in pre- to postoperative latency change scores (H4) were not. However, the statistical conclusion validity of these results is threatened by a lack of statistical power given the data source study’s relatively small sample size. Future studies will benefit from an increase in sample size to increase statistical power and reduce the threat to statistical conclusion validity.

Novelty effect poses a threat to the construct validity of this study. Novelty effect references the potential impact that a study participant’s skepticism or enthusiasm about participating in a new assessment technique can have on the results of initial assessment relative to follow-up assessment (Polit and Beck, 2017). For example, during the data source study, a participant may have been either more skeptical or enthusiastic when participating in
preoperative neurocognitive assessments than they were when participating in postoperative assessments as a result of novelty effect. Future studies may consider familiarizing study participants with the study’s planned neurocognitive assessment techniques prior to the baseline preoperative assessment in order to mitigate potential influence of novelty effects on study outcomes to enhance conclusion validity.

The study’s sample poses a threat the external validity of this study. External validity refers to the generalizability of the sample population’s results to the target population (Polit and Beck, 2017). As previously mentioned, the data source study’s sample population was a convenience sample of older surgical patients presenting to the PACE clinic at a single academic medical center. The sample is reasonably diverse given the relatively small number of participants available from the data source study including: male and female gender, two ethnic groups, ages ranging from 66-82, and four different surgical services. However, this sample is not ideally representative of the diversity among the target population (i.e., older surgical patients throughout the U.S.). Future studies could consider utilizing a combination of quota sampling and stratified randomization to obtain a sample population that better represents the target population to enhance external validity (i.e., generalizability of the study’s results).

Conclusions and Recommendations for Future Research

This study evaluated potential relationships between P300 AEPs and MoCA scores and differences in pre- to postoperative P300 AEP change scores between participants who received two or more PNMMA adjunct medications versus those who did not. The ultimate goal of this study was to contribute to the state of the science in search of a perioperative neurocognitive assessment that is rapid, easily-administrable, valid, reliable, automatically scored, void of language, cultural, and education bias and cost-efficient (Axley & Schenning, 2015). Such an
assessment is needed as the brain, anesthesia’s primary target, is limitedly assessed within the perioperative setting, perioperative cognitive morbidity among older surgical patients is common and costly, and perioperative brain health is a public health and research priority (American Society of Anesthesiologists, 2019).

In this study’s sample, an association between participants’ P300 AEPs and MoCA scores was not identified. However, Berger et al. (2018) reported that there is insufficient data to report sensitivity and specificity for MoCA in the perioperative setting and that MoCA has an inherent education bias. Rossetti et al. (2017) identified that several components of the MoCA and previously established cut-off points for cognitive impairment are not well suited for African Americans. P300 AEP derived neurobiomarkers may also assess a different aspect of brain health and provide alternative information related to a patient’s preoperative risk of POD versus the MoCA assessment.

A statistically significant difference in P300 amplitude change scores between participants who received two or more PNMMA medications versus those who did not was identified. Participants who received two or more PNMMA medications demonstrated a larger positive postoperative change in their P300 amplitude than participants who did not. This finding may point to, but does not confirm, the possibility that a synergistic neuroprotective effect could exist in older surgical patients receiving these medications. Future investigations with larger samples sizes and higher statistical power are needed to further explore these effects.

This study found no significant difference in participants’ P300 latency change scores between participants who received two or more PNMMA medications versus those who did not. This finding may call attention to the potential for P300 signal amplitude to serve as a perioperative neurophysiologic biomarker for trending cognitive function versus P300 latency.
However, this finding may also be the result of an underpowered study. In future studies, investigators may consider controlling for confounding perioperative factors that potentially impact P300 auditory evoked potentials (e.g., gender, age, length of anesthesia, pain, and emotional state at the time of assessment) as the clinical utility of these potential biomarkers is refined.

Pending further investigation, EEG-based neurobiomarkers may assist the development of perioperative brain health protection protocols that reduce the incidence and/or severity of perioperative neurocognitive disorders in older surgical patients. First, future research may consider evaluating the relationship between P300 AEPs and MoCA scores while controlling for the impact of potential ethnic and/or education biases on MoCA scores. Second, investigators may consider evaluating P300 amplitude as a perioperative neurocognitive trend metric while controlling for potentially confounding perioperative factors. Future research may also consider the potential utility of alternative EEG-based neurobiomarkers such as peak alpha frequencies or theta/beta ratios. Future studies will benefit from an increase in sample size and resulting increase in statistical power.

Investigation in search of a perioperative neurocognitive assessment that is rapid, easily-administrable, valid, reliable, automatically scored, void of language, cultural, and education bias and cost-efficient needs to be continued. The brain, anesthesia’s primary target, is currently poorly assessed within the perioperative setting. Perioperative cognitive morbidity among older surgical patients remains an all too common and costly phenomenon needing to be addressed. Until a perioperative cognitive screening tool capable of 1) predicting POD risk and stratifying patients into risk categories, 2) detecting mild cognitive impairments currently missed by brief cognitive screening tools (e.g., MoCA, Mini-Cog©, and CAM), and 3) objectively tracking the
progression of postoperative cognitive changes over time, reducing the incidence and severity of POD will likely remain a problematic public health and research priority with few clearly definitive perioperative brain health protection strategies for clinical application.
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Vita

L. Harold Barnwell, III was born on October 24, 1986, in Douglas, Georgia and is an American citizen. He graduated high school from Citizens Christian Academy, Douglas, Georgia in 2005. Harold earned a Bachelor of Science in Nursing, Magna Cum Laude, from Liberty University, Lynchburg, Virginia in 2009 and began his nursing career in the Cardiac Surgery Intensive Care Unit at Virginia Commonwealth University (VCU) Health System in Richmond, Virginia. He earned Master of Science - Doctor of Nurse Anesthesia Practice degrees, Summa Cum Laude, from VCU in 2014 and 2015 respectively, and subsequently began his practice as a Certified Registered Nurse Anesthetist (CRNA) with the VCU Health System. Harold joined the VCU Department of Nurse Anesthesia as an affiliate faculty member in 2015 and full time as an assistant professor in 2017 where he serves as the Assistant Director of Doctoral Education. Harold was awarded the Richard G. Ouellette Doctoral Research Fellowship from the American Association of Nurse Anesthetists (AANA) Foundation in 2020 to support his work investigating perioperative brain health among older surgical patients.
Appendix A

The Montreal Cognitive Assessment (MoCA)

<table>
<thead>
<tr>
<th>VISUOSPATIAL/EXECUTIVE</th>
<th>Copy cube</th>
<th>Draw CLOCK (Ten past eleven) (3 points)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>/5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NAMING</th>
<th></th>
<th></th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>/3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MEMORY</th>
<th>Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.</th>
<th>FACE</th>
<th>VELVET</th>
<th>CHURCH</th>
<th>DAISY</th>
<th>RED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1ST TRIAL</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>2ND TRIAL</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>NO POINTS</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATTENTION</th>
<th>Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order. Subject has to repeat them in the backward order.</th>
<th>[ ]</th>
<th>[ ]</th>
<th>[ ]</th>
<th>[ ]</th>
<th>[ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1ST TRIAL</td>
<td>2 1 8 5 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2ND TRIAL</td>
<td>7 4 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NO POINTS</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LANGUAGE</th>
<th>Repeat: I only know that John is the one to help today.</th>
<th></th>
<th></th>
<th>[ ]</th>
<th></th>
<th>[ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The cat always hid under the couch when dogs were in the room.</td>
<td></td>
<td></td>
<td>[ ]</td>
<td></td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>FLUENCY. Name maximum number of words in one minute that begin with the letter F.</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>NO POINTS</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABSTRACTION</th>
<th>Similarity between e.g. orange - banana = fruit - __________</th>
<th></th>
<th>[ ]</th>
<th>[ ]</th>
<th>[ ]</th>
<th>[ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Train - bicycle</td>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>Watch - ruler</td>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>NO POINTS</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DELAYED RECALL</th>
<th>Memory Index Score (MIS) [MIS] Has to recall words WITH NO CUE</th>
<th>[ ]</th>
<th></th>
<th>[ ]</th>
<th>[ ]</th>
<th>[ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X1 Category cue</td>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>X2 Multiple choice cue</td>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>MIS = 15</td>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>NO POINTS</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ORIENTATION</th>
<th>Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City</th>
<th></th>
<th>[ ]</th>
<th>[ ]</th>
<th>[ ]</th>
<th>[ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIS: [ ]/15 (Normal = 26/30) Add 1 point if &lt;12 yr edu</td>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>TOTAL [ ]/30</td>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

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Training and Certification are required to ensure accuracy

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Appendix B

The Mini-Cog® Assessment

Instructions for Administration & Scoring

ID: Date:

Step 1: Three Word Registration

Look directly at person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are [select a list of words from the versions below]. Please say them for me now." If the person is unable to repeat the words after three attempts, move on to Step 2 (clock drawing).

The following and other word lists have been used in one or more clinical studies. For repeated administrations, use of an alternative word list is recommended.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Banana</td>
<td>Leader</td>
<td>Village</td>
<td>River</td>
<td>Captain</td>
<td>Daughter</td>
</tr>
<tr>
<td>Sunrise</td>
<td>Season</td>
<td>Kitchen</td>
<td>Nation</td>
<td>Garden</td>
<td>Heaven</td>
</tr>
<tr>
<td>Chair</td>
<td>Table</td>
<td>Baby</td>
<td>Finger</td>
<td>Picture</td>
<td>Mountain</td>
</tr>
</tbody>
</table>

Step 2: Clock Drawing

Say: "Next, I want you to draw a clock for me. First, put in all of the numbers where they go." When that is completed, say: "Now, set the hands to 10 past 11."

Use preprinted circle (see next page) for this exercise. Repeat instructions as needed as this is not a memory test. Move to Step 3 if the clock is not complete within three minutes.

Step 3: Three Word Recall

Ask the person to recall the three words you stated in Step 1. Say: "What were the three words I asked you to remember?" Record the word list version number and the person's answers: __________  __________  __________

Word List Version:  Person's Answers: __________  __________  __________

Scoring

<table>
<thead>
<tr>
<th>Word Recall: _____ (0-3 points)</th>
<th>1 point for each word spontaneously recalled without cueing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clock Draw: _____ (0 or 2 points)</td>
<td>Normal clock = 2 points. A normal clock has all numbers placed in the correct sequence and approximately correct position (e.g., 12, 3, 6 and 9 are in anchor positions) with no missing or duplicate numbers. Hands are pointing to the 11 and 2 (11:10). Hand length is not scored. Inability or refusal to draw a clock (abnormal) = 0 points.</td>
</tr>
<tr>
<td>Total Score: _____ (0-5 points)</td>
<td>Total score = Word Recall score + Clock Draw score. A cut point of &lt;3 on the Mini-Cog® has been validated for dementia screening, but many individuals with clinically meaningful cognitive impairment will score higher. When greater sensitivity is desired, a cut point of &lt;4 is recommended as it may indicate a need for further evaluation of cognitive status.</td>
</tr>
</tbody>
</table>

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References


### Appendix C

The Confusion Assessment Method (CAM) Short Form

#### CONFUSION ASSESSMENT METHOD (CAM) SHORT FORM WORKSHEET

<table>
<thead>
<tr>
<th>EVALUATOR:</th>
<th>DATE:</th>
</tr>
</thead>
</table>

**I. ACUTE ONSET AND FLUCTUATING COURSE**

<table>
<thead>
<tr>
<th>a) Is there evidence of an acute change in mental status from the patient's baseline?</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
</table>

| b) Did the (abnormal) behavior fluctuate during the day, that is tend to come and go or increase and decrease in severity? | No | Yes |

**II. INATTENTION**

Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said?

| No | Yes |

**III. DISORGANIZED THINKING**

Was the patient’s thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

| No | Yes |

**IV. ALTERED LEVEL OF CONSCIOUSNESS**

Overall, how would you rate the patient’s level of consciousness?

- Alert (normal)
- Vigilant (hyperalert)
- Lethargic (drowsy, easily aroused)
- Stupor (difficult to arouse)
- Coma (unarousable)

Do any checks appear in this box?

| No | Yes |

If all items in Box 1 are checked and at least one item in Box 2 is checked a diagnosis of delirium is suggested.

Appendix D

WAVi™ Medical System Patent

(12) United States Patent
Oakley et al.

(10) Patent No.: US 9,854,988 B2
(45) Date of Patent: Jan. 2, 2018

(54) APPARATUS, SYSTEMS AND METHODS FOR RECEIVING SIGNALS FROM A HUMAN SUBJECT’S BRAIN

(71) Applicant: WAVI Co., Boulder, CO (US)

(72) Inventors: David Oakley, Boulder, CO (US); Edward Altshuler, Dacono, CO (US); Scott Seamans, Newport Beach, CA (US)

(73) Assigned to: WAVI Co., Boulder, CO (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 15/163,202

(22) Filed: May 24, 2016

(65) Prior Publication Data

Related U.S. Application Data


(51) Int. CL
A61B 5/0478 (2006.01)
A61B 5/0476 (2006.01)
A61B 5/090 (2006.01)

(52) U.S. CL
CPC A61B 5/0478 (2013.01); A61B 5/0476 (2013.01); A61B 5/0803 (2013.01); A61B 5/0814 (2013.01); A61B 5/083 (2013.01); A61B 5/0831 (2013.01);
A61B 5/0843 (2013.01); A61B 25/00444 (2013.01)

(56) Field of Classification Search
CPC A61B 5/0478; A61B 5/0803; A61B 5/0814; A61B 5/083; A61B 5/0831; A61B 25/00444; A61B 25/02/046
USPC 600/383, 544-545
See application file for complete search history.

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Primary Examiner — Lee S Cohen
Assistant Examiner — Erin M Cardinal
(74) Attorney, Agent, or Firm — E. Randall Smith; E. Randall Smith, PC

(57) ABSTRACT
Apparatus and methods for use in connection with receiving signals from a human subject’s head through the scalp thereof includes a removable headset having a plurality of electrode stations and intermediate portions. Each electrode station includes an electrode aperture extending there-through and a biasing flap coupled to the headset and at least partially aligned over the associated electrode aperture. A plurality of removable electrodes is releasably engageable with the headset and configured to be releasably suspended within the electrode apertures and biased between the headset and the subject’s head by the associated biasing flaps.

59 Claims, 16 Drawing Sheets
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<table>
<thead>
<tr>
<th>U.S. PATENT DOCUMENTS</th>
<th></th>
</tr>
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<tbody>
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<tr>
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APPARATUS, SYSTEMS AND METHODS
FOR RECEIVING SIGNALS FROM A
HUMAN SUBJECT'S BRAIN


FIELD OF THE DISCLOSURE

The present disclosure relates generally to apparatus, systems and methods for receiving signals from a human subject’s brain.

BACKGROUND

Taking brain activity data, brainwave measurements or the like, such as with known (electroencephalographic) EEG technology, historically required attaching electrodes to shaved portions of a subject's scalp area and customizing the placement of each electrode for high conductivity in order to receive useful signals during the test. One solution to shaving a patient's head was to sew electrodes to an elastic cap that is fit tightly onto the subject's head, each electrode terminating permanently in a wire that is bundled with other wires and routed to an electrical connector.

Existing technology for receiving signals from a subject's brain is believed to possess one or more potential disadvantages. For example, in some instances with the use of known EEG headsets, an electrode positioned over an uneven, or indented, portion of the subject's head may not abut or conform thereto sufficiently to conduct an electrical signal from the scalp to a measuring device that is useful for the test. For another example, the hair style of the subject (e.g. cornrows) may not allow sufficient electrical conductivity from the scalp to each electrode. For still a further example, the solid cap typically covers the entire scalp area of the subject and therefore does not allow the administrator of the test to visually inspect or adjust the position of the cap or individual electrodes to make meaningful, timely adjustments to achieve sufficient electrical contact. In many cases, the caps fit tightly over the subject's hair and scalp and become soiled with dirt, oil, germs, etc., which may be transferred to subsequent subjects using the same headset. For still another possible example, the sew-in electrodes may not be removed or moved for improved contact and may not be easily replaced with a different size or style that better matches a subject's physiology. Yet other potential disadvantages of known technology will be apparent from the description below.

It should be understood that the above-described features, capabilities and disadvantages are provided for illustrative purposes only and are not intended to limit the scope or subject matter of the appended claims or those of any related patent application or patent. Thus, none of the appended claims or claims of any related application or patent should be limited by the above discussion or construed to address, include or exclude each or any of the above-cited features, capabilities or disadvantages merely because of the mention thereof herein.

Moreover, there exists a need for improved apparatus, systems and methods useful for receiving signals from a human subject’s brain having one or more of the attributes or capabilities described or shown in, or as may be apparent from, the other portions of this disclosure.

BRIEF SUMMARY OF THE DISCLOSURE

In some embodiments, the present disclosure involves apparatus for use in connection with receiving electroencephalographic (EEG) signals from a human subject's head through the scalp thereof. The apparatus includes a removable headset arranged and adapted to extend at least partially around the subject's head over at least part of the subject's scalp. The headset includes an inner side and an outer side, the inner side being closer to the subject's scalp when the headset is positioned least partially around the subject's head. The headset includes a plurality of electrode stations and a plurality of intermediate portions. The intermediate portions extend between the electrode stations and are shaped and sized to form open spaces therebetween. Each electrode station includes an electrode aperture extending therethrough from the outer side to the inner side of the headset. The headset further includes a plurality of non-conductive biasing flaps, each biasing flap being connected to the headset and at least partially aligned over one of the electrode apertures. The headset further includes at least one EEG signal transmission wire associated with the electrode stations for receiving EEG signals. In these embodiments, a plurality of removable electrodes are releasably engageable with the headset and useful to facilitate the transmission of EEG signals from the subject's head to at least one EEG signal transmission wire of the headset during use of the headset. Each electrode includes a top end, bottom end and at least one side extending therebetween. Each electrode is configured to be releasably suspended within one of the electrode apertures and biased between the headset and the subject's head by the associated biasing flap. A plurality of electrically-conductive, electrode covers constructed at least partially of flexible, liquid-absorbing material are arranged and adapted to receive EEG signals from the subject's head and transmit such signals to at least one the EEG signal transmission wire of the headset during use of the headset. Each electrode cover at least partially encapsulates an electrode and is laden with electrically-conductive liquid during use of the headset. Each biasing flap is configured to bias the associated electrode cover into contact with the subject's head to allow the associated cover to receive EEG signals from the subject's head.

In at least one embodiment, a method of using the above-described apparatus includes releasably suspending the plurality of electrodes along with their associated electrically-conductive, liquid laden, electrode covers within the respective associated electrode apertures in the headset. The headset is placed on the subject's head. At least some of the biasing flaps bias their associated electrodes in the direction of the subject's head independent of the other electrodes in the headset. At least some of the electrode covers receive useful signals from the subject's head and transmit the received signals to at least one EEG signal transmission wire in the headset.

In various embodiments, the present disclosure involves apparatus for use in connection with receiving electroencephalographic (EEG) signals from a human subject's head through the scalp thereof. The apparatus includes a removable headset arranged and adapted to extend at least partially around the subject's head over at least part of the subject's scalp, the headset including an inner side and an outer side,
the inner side being closest to the subject's scalp when the headset is positioned least partially around the subject's head. The headset includes a plurality of electrode stations and a plurality of intermediate portions extending between the electrode stations and shaped and sized to form open spaces therebetween. Each electrode station includes an electrode aperture extending therethrough from the outer side to the inner side of the headset. The headset further includes a plurality of non-conductive biasing flaps, each biasing flap being coupled to the headset and at least partially aligned over one of the electrode apertures. The headset further includes at least one EEG signal transmission wire associated with the electrode stations for receiving EEG signals.

In these embodiments, a plurality of removable electrodes are releasably engageable with the headset and useful to facilitate the transmission of EEG signals from the subject's head to at least one the EEG signal transmission wire of the headset during use of the headset. Each electrode includes a top end, bottom end, at least one side extending therebetween and at least one portion extending outwardly from at least one of the sides. The portion is arranged and adapted to selectively position the associated electrode relative to the associated electrode aperture. Each electrode is configured to be releasably suspended within one of the electrode apertures and biased towards the subject's head by the associated biasing flap. Each biasing flap includes a flap hole at least partially aligned over the associated electrode aperture. Each flap hole includes at least one groove configured to selectively retain at least one the protrusion of the associated electrode. When at least one protrusion is selectively secured in the groove of its associated biasing flap, the electrode is configured to be moveable with the biasing flap relative to the electrode aperture during use of the headset.

The present disclosure also includes embodiments of apparatus for use in connection with receiving electroencephalographic (EEG) signals from a human subject's head through the scalp thereof. A removable headset is arranged and adapted to extend at least partially around the subject's head over at least part of the subject's scalp. The headset includes an inner side and an outer side. The inner side is closer to the subject's scalp when the headset is positioned least partially around the subject's head. The headset includes a plurality of electrode stations and a plurality of intermediate portions extending between the electrode stations and shaped and sized to form open spaces therebetween. Each electrode station includes an electrode aperture extending therethrough from the outer side to the inner side of the headset.

In these embodiments, the headset further includes a plurality of biasing flaps. Each biasing flap is directly coupled to the headset and at least partially aligned over one of the electrode apertures. The headset further includes at least one EEG signal transmission wire associated with the electrode stations for receiving EEG signals. A plurality of removable electrodes are releasably engageable with the headset and useful to facilitate the transmission of EEG signals from the subject's head to at least one the EEG signal transmission wire of the headset during use of the headset. Each electrode includes a top end, bottom end and at least one side extending therebetween. Each electrode is configured to be releasably suspended within one of the electrode apertures and biased between the headset and the subject's head by the associated biasing flap. A plurality of electrode covers constructed at least partially of flexible, liquid-absorbing material are arranged and adapted to be electrically-conductive, receive EEG signals from the subject's head and transmit such signals to at least one the EEG signal transmission wire of the headset during use of the headset. Each electrode covers at least partially encapsulates an electrode and is laden with electrically-conductive liquid during use of the headset. Each biasing flap is configured to bias the associated electrode cover into contact with the subject's head to allow the associated cover to receive EEG signals from the subject's head.

In at least one embodiment, a method of using the immediately above-referenced apparatus includes releasably suspending the plurality of electrodes along with their associated electrically-conductive, liquid laden, electrode covers within the respective associated electrode apertures in the headset. The headset is placed on the subject's head. At least some of the biasing flaps bias their associated electrodes in the direction of the subject's head independent of the other electrodes in the headset. Each electrode cover is configured to receive EEG signals from the subject's head and transmit the received signals to at least one EEG signal transmission wire in the headset.

In some embodiments, the present disclosure involves apparatus for use in connection with receiving electroencephalographic (EEG) signals from a human subject's head through the scalp thereof. A removable headset is arranged and adapted to extend at least partially around the subject's head over at least part of the subject's scalp. The headset
includes an inner side and an outer side, the inner side being closest to the subject's scalp when the head is positioned at least partially around the subject's head. The head set further includes a plurality of electrode stations and a plurality of intermediate portions extending between the electrode stations and shaped and sized to form open spaces therebetween. Each electrode station includes an electrode aperture extending therethrough from the outer side to the inner side of the head set. The head set further includes a plurality of biasing flaps and at least first and second flap fasteners associated with each biasing flap. Each biasing flap is coupled to the head set and at least partially aligned over one of the electrode apertures. The flap fasteners are adapted to secure the associated biasing flap to the head set on opposite sides of the associated electrode aperture. The head set further includes at least one EEG signal transmission wire associated with the electrode stations for receiving EEG signals.

In these embodiments, a plurality of removable electrodes are releasably engageable with the head set and useful to facilitate the transmission of EEG signals from the subject's head to at least one the EEG signal transmission wire of the head set during use of the head set. Each electrode includes a top end, bottom end and at least one side extending therebetween. Each electrode is configured to be releasably suspended within one of the electrode apertures and biased between the head set and the subject's head by the associated biasing flap. A plurality of electrode covers constructed at least partially of flexible, liquid-absorbing material is arranged and adapted to be electrically-conductive, receive EEG signals from the subject's head and transmit such signals to at least one the EEG signal transmission wire of the head set during use of the head set. Each electrode cover at least partially encapsulates an electrode and is laden with electrically-conductive liquid during use of the head set. Each biasing flap is configured to bias the associated electrode cover into contact with the subject's head to allow the associated cover to receive EEG signals from the subject's head.

In at least one embodiment, a method of using the immediately above-referenced apparatus includes releasably suspending the plurality of electrodes along with their associated electrically-conductive, liquid laden, electrode covers within the respective associated electrode apertures in the head set. The head set is placed on the subject's head. At least some of the biasing flaps bias their associated electrodes in the direction of the subject's head independent of the other electrodes in the head set. At least some of the electrode covers receive useful signals from the subject's head and transmit the received signals to at least one EEG signal transmission wire in the head set.

In certain embodiments, the present disclosure involves apparatus for use in connection with receiving electroencephalographic (EEG) signals from a human subject's head through the scalp thereof. A removable head set is arranged and adapted to extend at least partially around the subject's head over at least part of the subject's scalp. The head set includes an inner side and an outer side, the inner side being closest to the subject's scalp when the head set is positioned at least partially around the subject's head. The head set also includes a plurality of electrode stations and a plurality of intermediate portions extending between the electrode stations and shaped and sized to form open spaces therebetween. Each electrode station includes an electrode aperture extending therethrough from the outer side to the inner side of the head set. The head set further includes a plurality of biasing flaps, each biasing flap being directly coupled to the head set and at least partially aligned over one of the electrode apertures. The head set further includes at least one EEG signal transmission wire associated with the electrode stations for receiving EEG signals.

In these embodiments, a plurality of removable electrodes is releasably engageable with the head set and useful to facilitate the transmission of EEG signals from the subject's head to at least one the EEG signal transmission wire of the head set during use of the head set. Each electrode includes a top end, bottom end, at least one side extending therebetween and at least one protrusion extending outwardly from at least one side. Each protrusion is arranged and adapted to selectively position the associated electrode relative to the associated electrode aperture. Each electrode is configured to be releasably suspended within one of the electrode apertures and biased towards the subject's head by the associated biasing flap.

In at least one embodiment, a method of using the immediately above-referenced apparatus includes releasably suspending the plurality of electrodes within the respective associated electrode apertures in the head set and placing the head set on the subject's head. At least some of the biasing flaps bias their associated electrodes in the direction of the subject's head independent of the other electrodes in the head set. The head set includes an inner side and an outer side, the inner side being closest to the subject's scalp when the head set is positioned at least partially around the subject's head. The head set further includes a plurality of electrode stations and a plurality of intermediate portions extending between the electrode stations and shaped and sized to form open spaces therebetween. Each electrode station includes an electrode aperture extending therethrough from the outer side to the inner side of the head set. The head set further includes at least one EEG signal transmission wire associated with the electrode stations for receiving EEG signals.

In these embodiments, a plurality of removable electrodes is releasably engageable with the head set and useful to facilitate the transmission of EEG signals from the subject's head to at least one the EEG signal transmission wire of the head set during use of the head set. Each electrode includes a top end, bottom end, at least one side extending therebetween and at least one protrusion extending outwardly from at least one side. Each protrusion is arranged and adapted to selectively position the associated electrode relative to the associated electrode aperture. Each electrode is configured to be releasably suspended within one of the electrode apertures and biased towards the subject's head by the associated biasing flap.
flaps bias their associated electrodes in the direction of the subject's head independent of the other electrodes in the headset.

Accordingly, the present disclosure includes features and advantages which are believed to enable it to advance the art of brain signal recovery technology. Characteristics and advantages of the present disclosure described above and additional features and benefits will be readily apparent to those skilled in the art upon consideration of the following detailed description of various embodiments, accompanying drawings and appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The following figures are part of the present specification, included to demonstrate certain aspects of various embodiments of this disclosure and referenced in the detailed description herein:

FIG. 1 is a rear view of an exemplary signal receiving headset system shown as it would be positioned on a human subject's head in accordance with an embodiment of the present disclosure;

FIG. 2 is a front view of the exemplary headset system shown in FIG. 1;

FIG. 3 is a rear view of the exemplary headset system shown in FIG. 1;

FIG. 4 is a partial cross-sectional view of part of the exemplary headset system of FIG. 1 showing an exemplary electrode is an exemplary retracted position relative to the illustrated exemplary electrode aperture;

FIG. 5 is a partial cross-sectional view of part of the exemplary headset system of FIG. 1 showing the exemplary electrode of FIG. 4 in an exemplary extended position relative the illustrated exemplary electrode aperture;

FIG. 6 is a partial side view of an exemplary intermediate portion of an embodiment of a headset system having a fold-type flex point in accordance with an embodiment of the present disclosure;

FIG. 7A is a perspective view of an exemplary electrode biasing flap useful in the exemplary headset system shown in FIG. 1 in accordance with an embodiment of the present disclosure;

FIG. 7B is another perspective view of the exemplary electrode biasing flap shown in FIG. 7A;

FIG. 7C is yet another perspective view of the exemplary electrode biasing flap shown in FIG. 7A;

FIG. 8 is a side view of part of the part of the exemplary headset system of FIG. 1 showing an exemplary electrode biasing flap being manually stretched upwardly to show the underside thereof;

FIG. 9 is a perspective view of part of the exemplary headset system of FIG. 1 showing an exemplary electrode aperture;

FIG. 10A is a perspective view of the exemplary electrode useful in the exemplary headset system shown in FIG. 1 in accordance with an embodiment of the present disclosure;

FIG. 10B is a perspective view of the exemplary electrode shown in FIG. 10A with an exemplary electrode cover shown in partial cross-section in accordance with an embodiment of the present disclosure;

FIG. 10C is a perspective view of the exemplary electrode of FIG. 10B shown encapsulated by the exemplary illustrated electrode cover;

FIG. 11A is a perspective view of an exemplary tray of an exemplary electrode storage system in accordance with an embodiment of the present disclosure;

FIG. 11B is a perspective view of an exemplary electrode storage system in accordance with an embodiment of the present disclosure;

FIG. 12 is a perspective view of an exemplary signal receiving headset system shown positioned on a human subject's head in accordance with another embodiment of the present disclosure;

FIG. 13 is an exploded assembly view of part of the exemplary headset system of FIG. 12 showing an exemplary electrode station and related components;

FIG. 14 is a perspective view of the exemplary electrode station and related components of FIG. 13;

FIG. 15 is another perspective view of the exemplary electrode station and related components of FIG. 13;

FIGS. 16A-16B are side sectional views of part of the exemplary headset system of FIG. 12 showing an exemplary electrode being inserting into an exemplary electrode aperture in accordance with an embodiment of the present disclosure;

FIG. 16C is a side sectional view of the part of the exemplary headset system of FIG. 12 shown in FIGS. 16A-16B showing the illustrated exemplary electrode being biased between an exemplary electrode biasing flap and a subject's head in accordance with an embodiment of the present disclosure;

FIG. 17 is a top partially-disassembled view of the exemplary headset system shown in FIG. 12;

FIG. 18 is a perspective view of an exemplary signal receiving headset system shown positioned on a human subject's head in accordance with another embodiment of the present disclosure;

FIGS. 19A-19B are side sectional views of part of the exemplary headset system of FIG. 18 showing an exemplary electrode being inserting into an exemplary electrode aperture in accordance with an embodiment of the present disclosure;

FIG. 19C is a side sectional view of the part of the exemplary headset system of FIG. 18 shown in FIGS. 19A-19B showing the illustrated exemplary electrode being biased between an exemplary electrode biasing flap and a subject's head in accordance with an embodiment of the present disclosure;

FIG. 20A is a side view of a portion of the electrode system shown in FIG. 12 showing an exemplary tighten in accordance with an embodiment of the present disclosure;

FIG. 20B is a rear view of a portion of the electrode shown in FIG. 20A;

FIG. 21A is a side view of the exemplary electrode shown in FIG. 10A;

FIG. 21B is a top view of the exemplary electrode of FIG. 21A;

FIG. 22 is a perspective view of an exemplary electrode in accordance with another embodiment of the present disclosure;

FIG. 23 is a side view of an exemplary electrode in accordance with another embodiment of the present disclosure;

FIG. 24A is a side view of an exemplary electrode cover in accordance with an embodiment of the present disclosure;

FIG. 24B is a top view of the exemplary electrode cover of FIG. 24A;

FIG. 25 is a side view of an exemplary electrode cover in accordance with another embodiment of the present disclosure.
FIG. 26A is a perspective view of an exemplary electrode retention ring utilized in various embodiments of lead systems in accordance with one or more embodiments of the present disclosure; and
FIG. 26B is a perspective view of part of the exemplary electrode retention ring shown in FIG. 26A.

DETAIL DESCRIPTION OF PRESENTLY PREFERRED EMBODIMENTS

Characteristics and advantages of the present disclosure and additional features and benefits will be readily apparent to those skilled in the art upon consideration of the following detailed description of exemplary embodiments of the present disclosure and referring to the accompanying figures. It should be understood, however, that appended drawings, being example embodiments, are not intended to limit the claims of this patent application or any patent or patent application claiming priority hereto. On the contrary, the intention is to cover all modifications, equivalents and alternatives falling within the spirit and scope of the claims. Many changes may be made to the particular embodiments herein described without departing from such spirit and scope.

In showing and describing preferred embodiments in the appended figures, common or similar elements are referenced with like or identical reference numerals or are apparent from the figures and/or the description herein. When multiple figures refer to a component or feature with the same reference numeral, any description herein of the component or feature with respect to any of the figures applies equally to the other figures to the extent such description does not conflict with a description herein of the other figure(s). The embodiments shown in the figures are illustrated for simplicity and clarity and have not necessarily been drawn to scale. Also, common but well-understood components useful or necessary in the illustrated embodiments may not be depicted in the appended figures in order to facilitate a less obstructed view of other depicted features. Certain features and certain views of the figures may be shown exaggerated in scale or in schematic in the interest of clarity and conciseness.

As used herein and throughout various portions (and headings) of this patent application, the terms “inventor,” “present invention,” and/or variations thereof, as used herein and in the appended claims are intended to mean every possible embodiment encompassed by this disclosure or any particular claim(s). Thus, the subject matter of each such reference should not be considered as necessary for, or part of, every embodiment hereof, or of any particular claim(s) merely because of such reference. The terms “coupled,” “connected,” “engaged” and the like, and variations thereof, as used herein and in the appended claims are intended to mean either an indirect or direct connection or engagement. Thus, if a first device couples to a second device, that connection may be through a direct connection, or through an indirect connection via one or more other devices and/or connections.

Certain terms are used herein and in the appended claims to refer to particular benefits. As one skilled in the art will appreciate, different persons may refer to a component by different names. The use of a particular or known term of art in the name of a component herein is not intended to limit that component to only the known or defined meaning of such term (e.g., nut). Further, this document does not intend to distinguish between components that differ in name but perform the same function, and the terms “comprising,” “including,” “and” and “having” may be used interchangeably. The following description is not to be taken in a limiting sense, but is made merely for the purpose of describing the general principles of exemplary embodiments. Additional embodiments of this disclosure are possible. The described features, structures, characteristics and other details of the present disclosure may be combined in any suitable manner in one or more embodiments. One skilled in the relevant art will recognize that the embodiments of the present disclosure may be practiced with or without one or more of the exemplary details provided herein, or with other methods, components, materials, and so forth.

Further, all numbers expressing dimensions, physical characteristics and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about.” Accordingly, unless explicitly indicated to the contrary, the numerical values set forth in the following specification and claims may vary depending upon the desired properties sought to be obtained by the practice of one or more embodiments of the disclosure. Moreover, all ranges disclosed herein are to be understood to encompass any and all subranges subsumed therein. For example, a stated range of “1 to 10” should be considered to include any and all subranges between (and inclusive of) the minimum value of 1 and the maximum value of 10; that is, all subranges beginning with a minimum value of 1 or more and ending with a maximum value of 10 or less, e.g., 1 to 6.3, or 5 to 10, or 2.7 to 6.1.

For the purposes of promoting an understanding of the principles of the present disclosure, reference will now be made to the embodiments illustrated in the drawings.

Referring initially to FIGS. 1-3, in an independent aspect of the present disclosure, an embodiment of a reusable, re-usable signal receiving head system 10 for receiving EEG signals (or other signals) from a human subject is shown. The exemplary system 10 includes a headset, or cap, 12 that is releasably securable at least partially around the subject’s head 98 over at least part of the subject’s scalp 102. As used herein, the terms “head,” “cranium” and the like are used interchangeably. The exemplary headset 12 has an inner side 13 closest to the subject’s scalp 102 when the headset 12 is positioned on the subject’s head 98 and an outer side 15 that faces away from the scalp 102. The cap 12 may have any suitable form, construction, configuration, components and operation. In this example, the cap 12 is a “webbed” cap and includes a plurality of electrode stations 14 and a plurality of intermediate passages or strips, 16, for capping the area 104 of the subject’s scalp.
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102 to be tested or measured (the "scalp test area") 104). The exemplary electrode stations 14 are associated with at least one signal transmission wire, or wire lead 70 (e.g., FIG. 4) carried by the cap 12. Each illustrated electrode station 14 includes an electrode aperture 20 and an electrode biasing flap 40. Each exemplary electrode aperture 20 extends through the helmet 12 from the outer side 15 to the inner side 13 thereof and is configured to suspend or carry a removable electrode 30 useful for facilitating the transmission of signals (e.g., EEG signals) from the subject's brain to one or more of the signal transmission wires 70. Typically, for EEG testing, the electrode apertures 20 are positioned at predetermined locations in the cap 12 for positioning the electrodes 30 at specific locations relative to the subject's brain. The illustrated biasing flap 40 is coupled to the outer side 15 of the helmet 12 and is partially aligned over the associated electrode aperture 20 and configured to abut, or grip, and bias the associated electrode aperture 30 in the direction of the subject's head 98.

The illustrated intermediate portions 16 generally extend between the electrode stations 14. While the portions 16 are also referred to herein as "strips" and may, in some instances, be elongated in shape, the portions 16 need not each take the shape of an elongated strip. Thus, as used herein, the terms "strip," "intermediate portion," and variations thereof generally mean a section of the cap 12 disposed between, or adjacent to, one or more stations 14.

Referring now to FIGS. 4-5, one of the exemplary electrodes 30 is configured to be releasably suspended in each electrode aperture 20 during use of the system 10. In this embodiment, the electrodes 30 are not glued or bonded to the helmet 12. Each illustrated electrode 30 includes a top end 35 and a bottom end 34, at least one side 34 extending therebetween, and at least one outer side surface 32 extending at least partially along the side 31(s). The exemplary electrode 30 is configured to be biased between the helmet 12 and the subject's head 98 by its associated biasing flap 40. The electrode 30 and/or one or more components related thereto are configured to receive signals (e.g., EEG signals) from the subject's brain and transmit such signals to at least one of the wire leads 70 of the helmet 12.

In this embodiment, each electrode 30 is at least partially encapsulated by an electrode socket, or cover, 50 constructed at least partially of flexible, electrically-conductive liquid absorbing material. During use of the illustrated helmet 12, each cover 50 is adapted to be dipped in an electrically-conductive liquid 90, electrically-conductive, at least partially sandwiched (by its associated biasing flap 40) between its associated electrode 30 and the subject's head 98 to contact with the subject's scalp test area 104 to receive signals (e.g., EEG signals) from the subject's head 98 and transmit them to at least one wire lead 70 of the helmet 12. As used herein, the terms "liquid" and variations thereof mean sufficiently covered, soaked, saturated or near-saturated with one or more electrode wetting agents to allow the laden component to receive useful signals from the subject's brain through the head 98 and scalp 102 thereof. A useful signal is one that may be meaningfully used in the desired test analysis (e.g., EEG measurement/testing/analysis). As used herein, the terms "electrically-conductive liquid," and variations thereof mean and refer to liquids, gels and other suitable chemical combinations or formulations having properties that allow a component laden therewith to receive useful signals from the subject's head 98 and scalp 102. For example, each cover 50 may include a bottom end 34 that is electrically-conductive to an exterior side surface 31 thereof. The exemplary bottom end 32 is configured to electrically-conductively engage the subject's head 98 to receive EEG signals therefrom, and the side surface 31 electrically conducts the received signals to one or more wire leads 70 in the helmet 12.

In various embodiments, the electrodes 30 and/or covers 50 may be reusable, disposable or both. In some embodiments, the electrode covers 50 may not be included.

Referring back to FIGS. 1-5, the helmet 12 and its related components may be constructed of any suitable material or combination of materials. For example, the cap 12 (e.g., electrode stations 14 and strips 16) and/or its related components or the outer layers thereof, may be constructed of at least partially of one or more non-absorbent, water-resistant or water-proof materials (e.g., closed-cell foam) and/or easy-to-clean material. If desired, the cap 12 may be constructed of a material that includes antimicrobial and/or biostatic agents. For example, depending upon the particular scenario, the stations 14 and strips 16 may be constructed of plastic, rubber, foam, Crosite™, silicon, Trilene™, any other type of EVA or a combination thereof. Crosite™ is a proprietary closed-cell, anti-microbial, resin material developed for Cordis®, Inc. Trilene™ is a closed-cell copolymer developed by Scott Seaman for SoftScience™, Inc. Such construction of the cap 12 and related components may be useful, for example, to avoid the transfer of sweat, dirt, germs, microbes and/or bacteria from one or more subject's head 98 to the cap 12 during use of the helmet system 10 and/or to avoid problems caused thereby. For another example, such construction of the cap 12 and related components may render them reusable on multiple subjects with minimal or no cleaning, to meet sanitary standards or requirements, and/or any other desired purpose(s).

Still referring to FIGS. 1-5, the electrode stations 14 and strips 16 may have any suitable form, configuration, construction and operation. For example, the electrode stations 14 may be integrally formed with the strips 16. In the illustrated embodiment, the electrode stations 14 are shown integral to the strips 16, and have an overall generally diagonal shape and an average width that is greater than the average width of the exemplary strips 16. In other embodiments, the stations 14 may have an overall generally round, oval, rectangular, square or any other shape. In some embodiments, the stations 14 and strips 16 may be separate components that are interconnected in any suitable manner, such as with fasteners, adhesive or a combination thereof.

If desired, the strips 16 and/or stations 14 may be constructed of a material or combination of materials that is semi-rigid, conformable, resilient, elastic or a combination thereof. Also if desired, the strips 16 and/or stations 14 may be constructed and shaped to provide a desired mix of compressive, elastic, bending, flexing and conforming properties. For example, the width of the strips 16 may be selected to assist in providing the desired flexibility thereof. In the embodiment of FIGS. 1-5, the average width W1 (FIG. 2) of each illustrated strip 16 ranges from approximately ¼ inch to approximately ½ inch. However, the illustrated strips 16 may have any other desired width.

For another example, some or all of the electrode stations 14 and/or strips 16 may be formed of multiple layers. In this embodiment, the stations 14 and strips 16 are each formed of two layers, the electrode stations 14 having upper and lower layers 14a, 14b, and the strips 16 having upper and lower layers 16a, 16b. Multiple layers may be included for any suitable purpose. For example, multiple layers of stations 14 and/or strips 16 may provide the desired combination of stiffness and flexibility of the stations 14 and/or strips.
13. In this embodiment, two layers of flexible Cristolon™, Trilene™ or other antimicrobial material for the stations 14 and/or strips 16 may be provided to provide the desired combination of stiffness and flexibility of the headset 12. For another example, multiple layers may provide the desired protection of internally disposed components of the handset 12, such as the wire leads 70.

In many embodiments, some or all of the strips 16 may be constructed and configured to enhance the flexibility of the strips 16 and headset 12, allowing the strips 16 to be compressed or conform to the shape of the subject’s head 98 or a combination thereof. For example, one or more of the strips 16 may include one or more flex points 122 formed or provided therein. In the illustrated example, each flex point 122 is a bend in the outer layer 160 of some of the strips 16. In other embodiments, such as shown in FIG. 6, the illustrated flex point 122 is a bend or fold in the strip 16. Depending upon the configuration, the exemplary flex point 122 may allow the strips 16 to be moved upwardly or downwardly, such as when one end of the strip(s) 16, or headset 12, is squeezed or pushed towards its other end, avoiding twisting, bulging or buckling and/or assisting in ensuring uniformity of the cap 12 to the subject’s head 98.

Still referring to FIGS. 1-3, the electrode biasing flaps 20 may have any suitable form, configuration and operation. For example, the flaps 40 may be constructed at least partially of rubber, foam, foam rubber, a rubbery material, closed-cell foam, Cristolon™, impact-absorbing elastic, or any other material suitable for flexing and returning to its original position, resiliently biasing the electrode 30 downwardly towards the scalp 102 as desired and is otherwise suitable for use as part of the system 10. The flaps 40 may be positioned to partially, or entirely, cover, or align over, the respective electrode apertures 20 of their associated electrode stations 14. In this embodiment, each flap 40 is superimposed, or solid, above its associated electrode aperture 20 and aligns generally entirely over the aperture 20 (see also, FIG. 18). If desired, the flap 40 may include at least one nipple 43 (e.g., FIGS. 7A-C and FIG. 8) configured to insert and apply biasing forces to the top end 35 of an electrode 30.

In other embodiments, such as shown in FIGS. 12-15, the flap 40 may align over only part of the associated electrode aperture 20. In this example, the solid part of the exemplary flap 40 aligns over only the upper edge 20a of the aperture 20 because the flap 40 includes a flap hole 42. The flap hole 42 may have any suitable form, construction and configuration. In this embodiment, the flap hole 42 aligns over the electrode aperture 20 of the associated electrode station 14 and is configured to also suspend or carry the associated electrode 30. The flap hole 42 may also have any desired operation. For example, the flap hole 42 may be large enough to allow the passage of an electrode 30 therethrough and/or configured to assist in the positioning of the electrode 30 (e.g., FIGS. 16A-C), such as will be described further below.

Referring again to FIGS. 4-5, the flaps 40 may be engaged with the headset 12 in any suitable manner. For example, each flap 40 may be releasably or permanently fastened to an electrode station 14 and/or one or more strips 16 with flap fasteners 48. The flap fasteners 48 may have any suitable form, configuration, construction and operation. In this embodiment, the flap fasteners 48 are barbed, or arrow-shaped, extensions 49 integrally formed in the flap 40 on opposing sides thereof (also FIGS. 7A-C).

For connection with the cap 12, each illustrated extension 49 releasably extends into and engages a barb-receiving hole 47 formed in an electrode station 14 or strip 16 (see also, FIG. 8). In this embodiment, the barb-receiving holes 47 extend through both layers 14a, 14b of the associated station 14 (or layers 16a, 16b of the associated strip 16), such as to ensure a secure fit during stretching, biasing and other movement (e.g. twisting) of the flaps 40 when the headset 12 is in use. Further, in the exemplary fasteners 48 are removable from the headset 12. In other embodiments, the flap fasteners 48 may instead be permanently fixed to the headset 12.

In the embodiment of FIGS. 13 and 16A-C, the flap fasteners 48 are removable threaded plastic bolts 86 secured upwardly into receiving nuts 53. The electrode-biasing flaps 40 may instead, or also, be secured to the headset 12 using one or more adhesives. It should be noted that, in some embodiments, the headset 12 may include one or more springs or other forms of elastic elements used in combination with or instead of the flaps 40 for biasing the electrodes 30 downwardly into contact with the subject’s skin.

In another independent aspect of the present disclosure, referring back to FIGS. 4-5, the electrodes 30 may be inserted and removed from the headset 12 in any suitable manner. In some embodiments, the electrodes 30 are configured to be moveable into and out of the electrode apertures 20 in both directions. In the present embodiment, since the electrode biasing flap 40 is solid above the aperture 20, insertion or removal of the electrode 30 from the top, or outer side 15, of the headset 12 would require disengaging at least one of the flap fasteners 48 of each flap 40 to move the flap 40 away from the electrode aperture 20. Thus, the easier and quicker technique for inserting and removing the electrodes 30 in this embodiment is to insert the electrode 30 up into the electrode aperture 20 from below (from the inner side 13 of the headset 12) and remove it back down through the aperture 20 (in the direction of the inner side 13 of the headset 12). Similarly, in the embodiment of FIGS. 19A-C, the electrode 30 is inserted upwardly (arrows 58) into the aperture 20 and can be later removed downwardly in the opposite direction.

In the embodiment of FIGS. 13-16C, the illustrated electrodes 30 are also moveable in both directions into and out of the headset 12 because the flaps 40 each include a flap hole 42 through which the electrode 30 may pass. However, in this particular arrangement, the electrode 30 is preferably insertable into the headset 12 from the top, or outer side 15, of the headset 12 (arrows 60, FIGS. 16A-B) and removed in the same direction (toward the inner side 13 of the headset 12). The electrodes 30 of this embodiment are thus preferably moveable in one direction only.

Referring back to FIGS. 1-3, in another independent aspect of the present disclosure, in some embodiments, the exemplary headset 12 may include one or more base sections, or cap rings, 18 that at least partially aligns over and around a lower area of the subject’s head 98. The cap ring 18 may have any desired form, components and construction and may be configured for any desired purpose. For example, the cap ring 18 may be configured to provide tension to assist in the placement and/or positioning of the electrodes 30 relative to the scalp test area 104.

If desired, the cap ring 18 may include some of the electrode stations 14 interconnected by intermediate sections 16. In some embodiments, the cap ring 18 is at the front and 19 of the headset 12 (e.g., FIG. 2) may be open. In this example, the intermediate sections 16 at the front and 19 along the cap ring 18 of the headset 12 are not connected, such as to provide the desired flexibility of the headset 12, assist in achieving a good fit to the subject’s head 98, and/or
other suitable purpose. In various embodiments, the cap rim 18 at the rear end 21 or either side 116, 117 of the headset 12, or a combination thereof, may be open (not shown). If the cap rim 18 is open at any location, one or more releasable connectors, such as a pair of mateable velcro straps, or snap connectors, may be included to adjustable connect the adjacent open sections of the rim 18, such as to assist in securing the headset 12 to the subject's hand 98.

In some embodiments, the cap 12 may be adjustably tightened around the circumference of the subject’s head 98 and/or along one or more sides thereof to achieve a desired fit or for any other desired purpose. The cap 12 may be adjustably tightened in any suitable manner. For example, the cap 12 may be adjustably tightened around the cap rim 18. Referring specifically to FIG. 3, in this embodiment, the cap 12 is configured with a closure mechanism, or tightener, 114 useful to assist in tensioning or positioning the headset 12 as desired on the subject’s head 98, moving the headset 12 along and around the head, adequately positioning the electrodes 30 (e.g., FIGS. 4-5) in desired (e.g., approximately perpendicular) relative to the scalp test area 104 without the need for a chinstrap, any other suitable purpose or a combination thereof.

The tightener 114 may have any suitable form, configuration, component or operation. For example, one or more wires, or cables, 112 extending from each side 116, 117 of the headset 12, or along the rim 18, may be selectively tightened and/or loosened. In the illustrated example, the tightener 114 includes a ratcheting spool 120 mounted on a platform 110 and upon which a cable 112 coupled to each side 116, 117 is wound. If desired, the platform 110 may be positioned proximate to the occipital area 106 of the subject’s head 98, such as for support and comfort. The exemplary ratcheting spool 120 is rotated in and tension the cable 112 and draw the headset sides 116, 117 toward the rear. If desired, the ratcheting spool 120 may be configured to also loosen the cable(s) 112. The ratcheting spool 120 may be constructed of any suitable material, such as plastic. For example, the ratcheting spool 120 may be a commercially available spool commonly used in sports equipment.

Still referring to FIG. 3, if desired, the cables 112 may be selectively connectable to the headset 12 at different positions to achieve the desired effect. In this embodiment, each cable 112 may be spliced into one among multiple receivers 113 disposed at different positions along the cap rim 18. In some embodiments, one or more cable channels 119 may be formed in the platform 110. Further, if desired, the cables 112 may extend through one or more guides, or pulleys, 118 (e.g., FIGS. 20A-2B). In various embodiments, the cable(s) 112 may be connected to a chin strap and/or comprise complementary Velcro® straps for tensioning to each other. Further alternate embodiments may include a helmet strap attached to each side 116, 117 of the headset 12 and releasably fastened by mating connectors. In yet other embodiments, a tightening 114 may be included.

Referring back to FIGS. 1-3, in another independent aspect of the present disclosure, the exemplary cap 12 may have a “webbed” configuration, or arrangement, to form open spaces between some or all of its structural members (e.g., stations 14, strips 16, etc.) for any suitable purpose. For example, the strips 16 (and stations 14) may form one or more web open areas 100 to allow for visual inspection of the scalp test area 104, the position of each electrode 30 relative to the head 98 and/or the contact interface 105 (e.g., FIGS. 4-5) therebetween, to determine if the electrode 30 (or related component(s)) is making sufficient contact with the scalp test area 104 to receive useful signals from the subject’s brain, any other suitable purpose or a combination thereof. As used herein, the terms “contact interface” and variations thereof means and refers to the point or area of contact between an electrode 30 or one or more components related thereto (e.g. electrode cover 50) and the scalp 102 where the electrode 30 (or related component(s)) receives signals from the subject’s brain. In this illustrated embodiment (e.g., FIGS. 4-5), the exterior side surface 51 of each electrode cover 50 and each contact interface 105 are visible through the open areas 100.

For another example, the web open area 100 may assist in allowing the portions 16 of the headset 12 to bend, conform, stretch, compress, and/or fold without buckling or bulging, such as when the cap 12 is tightened or tensioned around the subject’s head 98. Such flexibility of the cap 12 may, in at least some instances, allow the exemplary electrode stations 14 to be positioned substantially parallel to the scalp test area 104 and/or the electrodes 30 to be positioned substantially perpendicular to the scalp test area 104 (e.g., FIGS. 4-5).

The web open area(s) 100 may have any suitable size, configuration and orientation. In some embodiments, for example, the web open area(s) 100 of the cap 12 may occupy at least approximately 20%-60% or more of the total area between the various structural members (e.g., strips 16 and stations 14) of the cap 12. In the present embodiment, the web open areas 100 occupy at least approximately 50% of the total space encompassed by the headset 12 (see also, FIGS. 12 and 17-18).

Referring back to FIGS. 4-5, the exemplary headset system 10 may have any suitable arrangement for receiving signals from the subject’s brain. As indicated above, the present embodiment includes one or more wire leads 70 (e.g., EEG signal transmission wires) associated with the electrode stations 14 for receiving signals from the electrode 30 or related components (e.g., cover 50) therein and conveying the signals to a desired destination. The wire leads 70 may have any suitable form, configuration, construction and operation, and may receive the signals from the electrode 30 or related component(s) in any suitable manner and convey them to any desired destination. It should be noted that the measuring device 108, operation thereof and the electrical connection of the system 10 thereafter is not limiting upon the present disclosure. For example, the system 10 may include an electrical connector 107 (e.g., FIG. 3) for electrically coupling the wire leads 70 to the measuring device(s) 108 (e.g., laptop computer). If desired, the headset 12 may include numerous wire leads 70, which may be bundled and/or interconnected. In the illustrated embodiment, at least one wire lead 70 is electrically coupled to an electrically-conductive surface 22 provided in each electrode aperture 20 and which conductively engages the associated electrode 30 (or associated component(s)). For example, the illustrated electrically-conductive surface 22 is slidable, electrically-conducitively engaged by the exterior side surface 51 of the electrode cover 50 to receive the EEG signals therefrom.

As shown in FIGS. 16A-17, the wire lead 70 may include a station end 72 electrically coupled to the electrically-conductive surface 22 and a device end 74 electrically coupled to any suitable desired measuring device(s) 108 (e.g., laptop computer). If desired, the headset 12 may include numerous wire leads 70, which may be bundled and/or interconnected. In the illustrated embodiment, at least one wire lead 70 is electrically coupled to an electrically-conductive surface 22 provided in each electrode aperture 20 and which conductively engages the associated electrode 30 (or associated component(s)). For example, the illustrated electrically-conductive surface 22 is slidable, electrically-conductively engaged by the exterior side surface 51 of the electrode cover 50 to receive the EEG signals therefrom.

As shown in FIGS. 16A-17, the wire lead 70 may include a station end 72 electrically coupled to the electrically-conductive surface 22 and a device end 74 electrically coupled to any suitable desired measuring device(s) 108 (e.g., laptop computer). If desired, the headset 12 may include numerous wire leads 70, which may be bundled and/or interconnected. In the illustrated embodiment, at least one wire lead 70 is electrically coupled to an electrically-conductive surface 22 provided in each electrode aperture 20 and which conductively engages the associated electrode 30 (or associated component(s)). For example, the illustrated electrically-conductive surface 22 is slidable, electrically-conductively engaged by the exterior side surface 51 of the electrode cover 50 to receive the EEG signals therefrom.

As shown in FIGS. 16A-17, the wire lead 70 may include a station end 72 electrically coupled to the electrically-conductive surface 22 and a device end 74 electrically coupled to any suitable desired measuring device(s) 108 (e.g., laptop computer).
vided on an electrically-conductive ring 24 disposed in, or lining, the electrode aperture 20.

When included, the electrically-conductive ring 24 may have any suitable form, configuration and operation. For example, the illustrated ring 24 is rigid and includes first and second ring portions 24a, 24b which are snapped or friction-fit, and/or glued together. Further, the electrically-conductive ring 24 may have any desired construction as long as it allows the transmission of signals from an electrode 30 or related component(s) to at least one wire lead 70. In this embodiment, the ring 24 is constructed of tin, such as to provide sufficient electrical conductivity with low electrical noise, to minimally tamish and/or other suitable purposes(s). In other embodiments, the electrically-conductive ring 24 may be made of any other suitable metal, such as gold, silver, copper, or aluminum, or a carbon composite. In some embodiments, the electrically-conductive ring 24 may include a metal plating or surfacing. In various embodiments, the electrically-conductive ring 24 may be constructed of a combination of the aforementioned or other materials.

It should be noted that the electrically-conductive ring 24 may serve one or more additional purposes. For example, the electrically-conductive ring 24 may also serve as an electrode retention ring (46) for assisting in positioning the associated electrode 30, such as will be described further below (e.g., FIGS. 4-5 and FIG. 9).

Still referring to the embodiment of FIGS. 4-5, the wire leads 70 may conductively engage the electrically-conductive surface 22 in any suitable manner. In this particular configuration, the illustrated wire lead 70 is coupled to the electrically-conductive ring 24 via an electrically-conductive screw 71. However, the wire lead 70 could instead be soldered or coupled to the ring 24 in any other suitable manner, as desired.

The wire leads 70 may be positioned in or carried by the headset 12 in any suitable manner. In this embodiment, each wire leads 70 is at least partially or substantially hidden or sandwiched between the respective upper and lower layers 14a, 14b of the electrode stations 14 and the respective upper and lower layers 15a, 15b of the headset 12. In other embodiments, the wire leads 70 may be carried within the bridge 16. In yet other embodiments, the wire leads 70 may be carried internally within the stations 14 and 15, and strips 16 or otherwise coupled to the cap 12. In yet other embodiments, an wire harness comprising all the wire leads 70 may be enclosed within the cap 12 or affixed thereto.

In another independent aspect of the present disclosure, referring back to FIGS. 1-5, the electrodes 30 are biased into contact with the subject's head 98 to receive signals from the subject's brain in any suitable manner. In this embodiment, each electrode 30 is configured to be suspended within its associated electrode aperture 20 so that it effectively floats within a generally defined range of up-and-down motion relative to the aperture 20. At the same time, the exemplary biasing flap 40 provides downward biasing forces on the electrode 30.

During use, each illustrated biasing flap 40 independently places downward biasing forces on its associated electrode 30, while concurrently, the subject's head 98 typically places upward forces (e.g., to conform substantially to the 30). As such, individual exemplary electrode 30 freely floats (e.g., within a range of motion) relative to its associated aperture 20, the electrode 30 will automatically move into the appropriate up-and-down position between the biasing flap 40 and the subject's head 98 and relative to the headset 12 independent of all the other electrodes 30 in the headset 12. The position of each illustrated electrode 30 with thus be influenced or determined by the shape of the subject's head 98 at that location. Different electrodes 30 may assume different positions relative to the headset 12. Accordingly, since each exemplary electrode 30 fits the shape of the subject's head 98 at that location, the headset 12 may conform to the unique (typically uneven) shape of each subject's head 98. As compared to prior signal receiving headsets, the exemplary cap 12 may, for example, be more universally (fitable and useful, more easily adaptable to the unique shape of different subjects' heads 98, provide better electrode positioning and electrical contact with the subjects' scalp test areas 104, be easier and quicker to successfully use, be more reliable or a combination thereof.

Referring again to FIGS. 4-5, in many embodiments, the electrodes 30 may be moveable and positionable relative to the headset 12 between at least one retracted position (or range-of-motion) and at least one extended position (or range-of-motion) to assist in conforming the headset 12 to the shape of each subject's head 98, provide better electrode positioning and electrical contact with the subjects' scalp test areas 104, be easier and quicker to successfully use, be more reliable, any other desired purpose or a combination thereof. It should be noted that during use of this embodiment, in all retracted and extended positions the electrode 30 is biased in the direction of the subject's head 98 by its associated biasing flap 40.

In a retracted position, each exemplary electrode 30 is higher in its associated electrode aperture 20, and the bottom end 34 of the electrode 30 is closer to the inner side 13 of the headset 12, than in its extended position(s). In other words, in a retracted position, more of the illustrated electrode 30 lies above the electrode aperture 20 than in its extended position(s). The exemplary retracted position(s) may be useful, for example, as the initial position of the electrode 30 during placement of the cap 12 on the subject's head. In many instances, the retracted position(s) of some, many or all the electrodes 30 may provide sufficient electrical conductivity with the subject's head 98, so that movement into an extended position may be unnecessary.

Still referring to FIGS. 3 and 4, an extended position, more of the exemplary electrode 30 lies below the aperture 20 than above the aperture 20. The extended position(s) may be desirable or necessary, for example, for any electrodes 30 not making sufficient electrical contact with the scalp test areas 104 after the cap 12 is fitted onto the subject's head 98.

The electrodes 30 may be moveable between retracted and extended positions in any desired manner. For example, to move an exemplary electrode 30 from a retracted position to an extended position, the flaps 40 and electrode 30 may be pushed downwardly from above. To move the illustrated electrode 30 from an extended position to a retracted position, the bottom end 34 of the electrode 30 may be pushed upwardly (See also, FIGS. 18-19C).

Now referring to FIGS. 10A-C, in some embodiments, the electrode 30 includes one or more protrusions 36 extending outwardly from at least one side 31 thereof. The protrusion(s) 36 (e.g., FIGS. 4-5) may be useful, for example, to assist in selectively positioning the electrode 30 relative to the headset 12 and/or subject's scalp 102 (e.g. height-wise and angle-wise, e.g. to conform substantially to the scalp 102), provide more flexibility and greater degrees of freedom in the up-and-down movement of the electrode 30, assist in the movement of the electrode 30 between retracted and extended positions, secure the electrode 30 into one or more retracted or extended positions,
provide a distinct range of motion of the electrode 30 in multiple respective retracted and extended positions, any other suitable purpose or a combination thereof.

The protrusions 36 may have any suitable form, configuration and construction. For example, one or multiple adjacent protrusions 36 may extend partially or entirely around the outer side surface 32 of the electrode 30. In this embodiment, two aligned protrusions 36 form a circular ridge around the outer side surface 32 of the cylindrically-shaped electrode 30 at a desired height on the electrode 30. For example, the protrusion 36 may be spaced upwardly from the bottom end 34 of the electrode 30 by approximately \( \frac{1}{4} \) of the height of the electrode 30 to achieve the desired result(s) of use of the protrusion 36, such as described above. For some other examples, the protrusions 36 may be or include one or more rims, ledges, shells, cut-outs, uneven portions, buttons, hooks, pilings, channels or other-shaped members or portions extending at least partially around the side(s) 31 of the electrode 30. Further, when electrode covers 50 are included, the system 10 may be configured so that the covers 50 conform to the shape of the protrusions 36 of the associated electrodes 30 (e.g., FIGS. 10B-C). In other embodiments, if desired, the protrusion 36 may penetrate through the electrode cover 50.

The protrusions 36 may have any suitable operation. Referring again to FIGS. 4-5, in this embodiment, when an electrode 30 is in a retracted position, the protrusion 36 will be closer to the outer side 15 of the headset 12 than the inner side 13. When the exemplary electrode 30 is in an extended position, the protrusion 36 will be closer to the inner side 13 of the headset 12 than the outer side 15. If desired, the protrusion 36 may be useful to establish and/or secure the desired position of the electrode, such as in the extended and/or retracted positions. For example, the protrusion 36 may be engageable with the electrode aperture 20, or other component(s), in one or more positions. In some embodiments, the protrusion 36 may be configured to releasably selectively engage the upper edge 20a of the aperture 20 and/or the lower edge 20b of the aperture 20 (see also, FIGS. 13, 19B), one or more grooves 44 (e.g., FIG. 16B-C) or other protrusion-engagement surface(s) provided in the aperture 20 or other component (e.g., upper and lower edges 46a, 46b of an electrode retention ring 46 (see also, FIG. 19B)), or a combination thereof.

In the embodiment of FIGS. 16A-C, the protrusion 36 is selectively releasably engageable with a groove, or catch, 44 provided in the flip hole 42 of the biasing flap 40. In this example, the electrode 30 is insertable downwardly (arrow 60, FIGS. 16A-B) into the illustrated flip hole 42 to snap the protrusion 36 into releasable engagement with the illustrated groove 44. In this position, the exemplary electrode 30 is effectively anchored to the flip 40. As the illustrated flip 40 flexes, the electrode 30 moves, or floats up and down in and relative to the electrode aperture 20 in response to upward forces from the subject's scalp 102 during use (e.g., arrow 64, FIG. 16C).

In this embodiment, the electrode 30 is thus movable into only one engaged position, and the exemplary flap 40 serves the dual-purpose of biasing and retaining the electrode 30. However, in other embodiments, additional engaged positions may be provided, such as with multiple grooves 44 or other engagement surfaces in the flip hole 42 or other component. The use of one or more grooves 44 or other protrusion engagement surface(s) may be useful to selectively positioning the electrode 30 relative to the headset 12 and/or subject's scalp 102 (e.g., height-wise and angle-wise (e.g., to conform substantially perpendicularly to the scalp 102), provide a distinct range of motion of the electrode 30 relative to the headset 12, any other suitable purpose or a combination thereof.

Still referring to FIGS. 16A-C, if desired, the groove 44 or other protrusion engagement surface of the flip hole 42 may be formed in an electrode retention ring 46 disposed within, or lining, the flip hole 42. The retention ring 46 may have any suitable form, configuration and operation. In this embodiment, for example, the retention ring 46 is rigid, constructed of plastic, molded into the flip 46 and includes a textured outer surface 46e (e.g., FIGS. 26A-B) for gripping the flip hole 42 to secure them together.

In some embodiments, the groove, or catch, 44 may be configured (e.g., with one or more angled edges or polarized) to assist in selectively positioning the electrode 30 relative to the headset 12 and/or subject's scalp 102 (e.g., height-wise and angle-wise (e.g., to conform substantially perpendicularly to the scalp 102)), promote movement of the electrode 30 in a desired direction for removal (such as downwardly) or other purpose. In this example, once the electrode 30 is inserted and snapped into the groove 44 from above (from the outer side 15 of the headset 12), the electrode 30 may be easily, or only, removed by pushing downwardly on the electrode 30 to release it from the groove 44, flip hole 42 and electrode aperture 20. In other embodiments, the groove, or catch, 44 may be configured to promote or require (i) upward insertion and removal of the electrode 30 from underneath (from the inner side 13 of the headset 12), (ii) upward insertion and downward removal, (iii) downward insertion and upward removal, or (iv) unidirectional insertion and removal.

Referring back to the embodiment of FIGS. 4-5, in this example, the illustrated electrically-conductive ring 24 also serves as the electrode retention ring 46 and does not include a groove 44. In this example, the relationship of the illustrated electrode protrusion 36 relative to the electrode retention ring 46 determines whether the electrode is in a retracted or extended position. For example, the protrusion 36 may be shaped and sized so that it sits above the electrode retention ring 46 (closer to the upper edge 46a of the ring 46 than the lower edge 46b) when the electrode 30 is in a retracted position, and below the electrode retention ring 46 (closer to the lower edges 46a of the ring 46 (than the upper edge 46a) when the electrode 30 is in an extended position. From either position, with sufficient pressure on the exemplary electrode 30, the protrusion 36 is moveable between a retracted position and an extended position. Thus, the illustrated protrusion 36 is forcibly, selectively, slideable up and down through the retention ring 46. For example, the protrusion 36 may be designed to be movable through the ring 46 under only certain applied pressure. For example, when the protrusion is below the retention ring 46 (the electrode 30 in an extended position), the system 10 may be designed so that the typical or expected upward forces from the subject's head 98 during fitting and use of the headset 12 will not dislodge the protrusion 36 upwardly through the ring 46.

Still referring to FIGS. 4-5, in some embodiments, the protrusion 36 and/or the upper and/or lower edges 46a, 46b of the electrode retention ring 46 may be shaped to complement each other, such as to assist in selectively positioning the electrode 30 relative to the headset 12 and/or subject's scalp 102 (e.g., height-wise and angle-wise (e.g., to conform substantially perpendicularly to the scalp 102)), assist in the desired direction of insertion/removal of the electrode 30 into/from the headset 12, other suitable purpose or a combination thereof. For example, the outer curvature of the
21 protrusion 36 (e.g., FIG. 10A), may match the curvature of the edges 46a, 46b (e.g., FIG. 9) of the ring 46 so that the protrusion will seat in the upper and lower edges 46a, 46b in respective retracted and extended positions. In the illustrated embodiment, the upper and lower edges 46a, 46b of the electrode retention ring 46 are beveled (e.g., FIG. 9) to compliment the shape of the protrusion 36.

Also if desired, the movement of the protrusion 36 above or below the electrode retention ring 46 may provide additional positions for the electrode 30. In the present embodiment, the electrode 30 can freely move within a defined up and down range of motion above the electrode retention ring 46 among multiple retracted positions and below the electrode retention ring 46 among multiple extended positions.

In the embodiment of FIGS. 19A-C, the protrusion 36 is located proximate to the bottom end 35 of the electrode 30 and retracted engagement with the upper edge 46a of the retention ring 46 into and out of one extended position. In this embodiment, the electrode 30 is moveable within a defined range of motion in multiple extended positions (above the electrode aperture 20) due to the upward forces (arrow 64, FIG. 19C) placed upon it by the subject's head 98.

Referring now to FIGS. 21A-2B, the electrode 30 may have any suitable form, configuration, components, and operation. The electrode 30 may be a single unitary component or multiple interconnected units. For example, in the exemplary embodiment, the electrode 30 is a single unit having a generally cylindrical outer shape. Some other exemplary outer shapes of electrodes 30 are square, triangular, oval, stepped and rectangular. In FIG. 23, the exemplary electrode 30 has an upwardly-angled, flared outer shape, such as for ease of insertion from above into the flap hole 42 and/or electrode aperture 20. In other embodiments, the electrode 30 may have a downwardly-angled, flared outer shape, such as for ease of insertion from below into the electrode aperture 20 and/or flap hole 42.

In some embodiments, the electrode 30 is partially formed of memory foam (e.g., FIG. 23). Memory foam electrodes 30 may have any desired form, configuration and operation. For example, memory foam electrodes 30 may be used in a desired location on the head 98, such as portions with no hair (e.g., the forehead or on the entire head 98 of a bald subject). In some embodiments, some or all of the electrodes 30 may be configured to be useful without electrode cover 50. For example, the bottom end 34 of the electrode 30 may be electrically conductive to the outer side surface 32 thereof. In such embodiments, the bottom end 34 may electrically conductively contact the scalp 102 and receive signals from the subject's brain. These signals may then be electrically communicated to the outer side surface 32 of the electrode 30, then to the electrically-conductive surface 22 in the electrode aperture 20, and then to the lead wire 70.

Still referring to FIGS. 21A-2B, the electrode 30 may be constructed of any suitable material, such as plastic, rubber, paper, fiberglass, wood, material tolerant of one or more conductive solutions, carbon-containing material, or a combination thereof. In some embodiments, the electrodes 30 are constructed of fluid absorbing material, such as foam and/or electrically-conductive material, such as conductive polymer material.

In various embodiments, the top and/or bottom ends 35, 34 of the electrode 30 may be open, include one or more perforation or be closed. In the present embodiment, both the top end 35 and bottom end 34 are open. In the embodiment of FIGS. 13 and 22, the top end 35 of the electrode 30 is open, while the bottom end 34 is at least substantially closed (e.g., may include one or more perforations for engagement with an internally located flexible electrode stabilizing insert). In some embodiments, the bottom end 34 of the electrode 30 may be textured or rough, such as to improve contact and electrical conductivity with the scalp 102. The bottom end 34 may be rounded or beveled to expedite the skin to assist in attaining good electrical conductivity, other suitable purpose or a combination thereof.

Still referring to FIGS. 21A-2B, in some embodiments, the electrode 30 includes one or more cut-outs, or flex slots, 38. The cut-out(s) 38 may be included for any purpose, such as to allow the electrode 30 to flex during insertion and/or removal from the electrode aperture 20 and/or flap 40. For example, the cut-out(s) 38 may allow the electrode 30 to be easily squeezed and snaps into place, and once in place in the head 98, squeezed to be removed from the subject. The flex slots 38 may have any suitable form, configuration and operation. In the present embodiment, two cut-outs 38 extend from the bottom end 34 of the electrode 30 up to a desired location along the height of the side 31 (see also, FIGS. 4, 5, 10A-2B). The illustrated flex slots 38 may be useful, for example, for squeezing the electrode 30 proximate to its top end 35, or allowing the electrode 30 to flex therewithout, during upward insertion and downward removal of the electrode 30 into/from the electrode aperture 20.

In the embodiment of FIGS. 14 and 22, four cut-outs 38 are shown extending from the top end 35 of the electrode 30 up to a desired location along the height of the side 31. The flex slots 38 in this embodiment may be useful, for example, for squeezing the electrode 30 proximate to its top end 35, or allowing the electrode 30 to flex therewithout, during upward insertion and downward removal of the electrode 30 into/from the electrode apertures 20.

Now referring to FIGS. 10A-1C, the electrode cover 50 may have any suitable form, configuration, construction and operation. The cover 50 may or may not completely encapsulate the electrode 30 and may or may not be glued or otherwise secured to the electrode 30, as desired. When it is desired to secure the cover 50 to the electrode 30, any suitable technique may be used. For example, the cover 50 may include a draw string, elastic band(s) or the like that may be tightened to assist in retaining the cover 50 on the electrode 30. For another example, the cover 50 may be glued and/or heat-welded to the electrode 30. In some embodiments, the cover 50 may tightly fit and grip the electrode 30 without glue or any gripping mechanism.

In the present embodiment, the exemplary cover 50 completely encapsulates the electrode. The illustrated cover 50 has an upper sub-opening 54 for slipping the cover 50 over the bottom end 34 of the electrode 30 that is tucked into the open top end 35 of the electrode 30. The illustrated cover 50 is glued or heat-welded around the opening 54 to close off the opening 54 and may also be glued or heat-welded thereto or the interior of the electrode 30. In the embodiment of FIGS. 24A-B, the cover 50 will not completely encapsulate, and is not secured to, the electrode 30.

When the cover 50 is constructed of electrically-conductive liquid 90 absorbing material, the cover 50 may be constructed at least partially of cotton, natural or synthetic conductive material, fibers or fabric, any other liquid-absorbing and electrically-conductive material or a combination thereof. In some embodiments, multiple conductive fibers (not shown) may be woven into the cover 50 for lowering contact and/or path resistance. In various embodiments, the cover 50 may be at least partially constructed of
exfoliating material (e.g. nylon), as is known and used in beauty industry, and/or have a textured or rough surface at the bottom and 25 thereof.

Still referring to FIGS. 100-C, if desired, the cover 50 may have a seam 55 disposed at the bottom end 52 of the cover 50 (see also, FIG. 25). The seam 55 may have any suitable form, configuration and operation. For example, the seam 55 may accumulate more electrically-conductive liquid 90 than the remainder of the cover 50, extend farther into the subject’s hair and against the scalp 102 than the body of the cover 50, be course or thick and useful to exfoliate the subject’s scalp 102 if the electrode 30 is rotated or otherwise moved while in contact with the scalp 102, any other suitable purpose or a combination thereof.

Referring again to FIGS. 4-5, 12 and 18, in other independent aspects of the present disclosure, in some embodiments, the electrode 30 may be movable within the electrode aperture 20 as it engages the subject’s scalp 102. For example, the electrode 30 may be replaceable to pass through the subject’s hair and/or scrub, abrade or exfoliate one or more epidermal layers of the scalp 102 for improving electrical conductivity. As the exemplary electrode 30 is replaceable on the subject’s scalp 102, the electrode 30 (or cover 50 thereof) may be used to rub, scrub, clean or abrade the scalp 102 to exfoliate the scalp 102 or remove dead skin therefrom, such as to assist in achieving better electrical contact and conductivity. The use of an electrode 30 (with or without cover 50) to rub, exfoliate or prepare the scalp for use of the headset system 10, such as described above, could be instead of a blunt needle typically rubbed against the scalp to remove dead skin, exfoliate or otherwise prepare the scalp for use during such testing.

The electrodes 30 may be formed in different sizes, shapes and configurations. In some embodiments, the electrodes 30 may be replaceable on a per patient basis, such as for cleanliness, optimizing electrical conductivity (if they dry out or are calibrated for wetness) or other purpose. In various embodiments, different electrodes 30 may be used on the head 12 for a particular subject and/or at different locations in the cap 12, such as to improve electrical conductivity or for other reasons. For example, different sized, shaped or configured electrodes 30 may be provided to accommodate different electrode positions on the cap 12 for a particular subject to improve or optimize electrical conductivity at each location. For another example, electrodes 30 constructed of different materials and/or some with and some without covers 50 may be used for a particular subject.

For use of the exemplary systems 10, the electrodes 30 (or covers 50, when included) are laden with one or more electrode wetting agents to provide or enhance electrical conductivity.

Referring back to FIGS. 1-5, in another independent aspect of the present disclosure, an electrically-conductive liquid, or formula 90 may be placed upon each electrode 30 (and/or cover 50, when included) as the electrode wetting agent. For example, the electrically-conductive liquid 90 may be useful to lower contact resistance at the scalp and/or to lower path resistance for signal flow (e.g. arrows 109, FIG. 19C) from the bottom end 34 of the electrode 30 to wire 70 to a desired level. In many embodiments, the electrically-conductive liquid 90 may be designed to possess electric conductivity attributes that will allow or match the input impedance specification for the particular signal amplifier of the test (EEG or other brainwave measurement) system being used in some embodiments. For example, the electrically-conductive liquid 90 may be designed to possess electrical conductivity attributes that allow the electric path resistance for signal flow (e.g. arrows 109, FIG. 19C) to be maintained at less than 80 k ohms, and, in some instances, less than 40 k ohms and, in some instances, less than 5 k ohms impedance.

The electrically-conductive liquid 90 may have any suitable composition and properties. In accordance with various embodiments, the electrically-conductive liquid 90 includes a hair conditioner and/or an optical/contour lens solution. In some embodiments, such as when a gel would normally be used during the test, the electrically-conductive liquid 90 may include the hair conditioner, such as, for example a “leave-in” hair conditioner. This form of electrically-conductive liquid 90 may be combed into the hair after the test and the hair may be returned to its normal appearance. The use of hair conditioner in the electrically-conductive liquid 90 may also, in at least some situations, serve the function of nourishing the hair. The use of hair conditioner in the electrically-conductive liquid 90 may also allow typical subjects to resume their daily or nighttime activities without having to wash their hair. For example, if the test is conducted during a routine physical exam, the subject may be able to immediately return to work or his/her other activities, as opposed to having to first wash his/her hair.

When used in the electrically-conductive liquid 90, the hair conditioner may have any suitable ingredients and liquid properties. One example presently commercially available leave-in conditioner that could be included, or used as, the electrically-conductive liquid 90 in some embodiments is “PAUL MITCHELL® THE CREAM® Leave-in Conditioner and Styler”, having the following ingredients: Water, PVP, Glycerin, Yeast (Sauer) Extract, Methyl Gluceth 10, Stearamonolaurin Chloride, Simmondsia Chinensis (Jojoba) Seed Oil, Carthamus Tinctorius (Safflower) Seed Oil, Ammonium Hydrogen Carbonate, Bisaminon PEUG/PG 4/3 Aminomethyl PG Propyl Dimethicone, Panthenol, Ethylhexyl Methoxycinnamate, Benzophenone 4, Guar Hydroxypropyltrimonium Chloride, Cetyl Alcohol, Hydroxyethylcellulose, Polyisobutene 60, Phenoxetanol, C11-15 Pareth 7, Trideceth 12, Laureth 9, Citric Acid, Methylparaben, Propylparaben, Disodium EDTA, Diazolidinyl Urea, Fragrance, Hexyl. In various embodiments, an exemplary electrically-conductive liquid 90 may include any particular two or more of the above-listed ingredients.

Another example presently available leave-in conditioner that could be included, or used as, the electrically-conductive liquid 90 in various embodiments is “Generic Value Products Cream”, presently available at Sally Beauty Supply, LLC in Sally item No. SHS-264003 and having the following ingredients: Water (Aqua), PVP, Glycerin, Yeast Extract, Methyl Gluceth 10, Stearamonolaurin Chloride, Simmondsia Chinensis (Jojoba) Seed Oil, Carthamus Tinctorius (Safflower) Oil, Ammonium Hydrogen Carbonate, Bisaminon PEUG/PG 4/3 Aminomethyl PG-Propyl Dimethicone/Hydroxyethyl Coraminium (White Ginger)/PEG-12 Dimethicone, Panthenol, Ethylhexyl Methoxycinnamate, Benzophenone 4, Guar Hydroxypropyltrimonium Chloride, Cetyl Alcohol, Cetearyl Alcohol, Hydroxyethylcellulose, Polyisobutene 60, Phenoxetanol, C11-15 Pareth 7, Trideceth 12, Laureth 9, Citric Acid, Fragrance (Parfum), Methylparaben. In many embodiments, an exemplary electrically-conductive liquid 90 may include any particular two or more of the above-listed ingredients. However, the present disclosure is not limited to these particular examples.

In some embodiments, the electrically-conductive liquid 90 includes optical/contour lens solution. In various embodiments,
ments, the optical/contact lens solution may provide eye soothing and/ or disinfecting benefits and/or be less sticky.

When included in the electrically-conductive liquid 90, the optical/contact lens solution may have any suitable ingredients and liquid properties. For example, one presently commercially available optical/contact lens solution that could be included in some embodiments of the electrically-conductive liquid 90 is "Aqua Sensitive Multi-Purpose Solu-
tion" by Bausch & Lomb Incorporated and having the ingredients of a sterile, isotonic solution that contains boric acid, edetic disodium, poloxamine, sodium borate and sodium chloride; preserved with DVMIP (polyvinylpro-
pyl biguanide) 0.00005%. In many embodiments, an exemplary electrically-conductive liquid 90 may include any particular two or more of the above-listed ingredients. However, the present disclosure is not limited to this particular example.

The electrodes 30 (or covers 50) may be laden with the electrically-conductive liquid 90 in any suitable manner. In some embodiments, the electrodes 30 may be first inserted into the headset 12 and then laden with electrically-conduc-
tive liquid, such as with a squirt bottle or other applicator. In other embodiments, for example, the electrodes 30 (with or without the covers 50) may be pre-packaged wet with the electrically-conductive liquid 90. For example, the pre-
packed electrodes 30 may be stored in a sealed plastic pouch. For another example, in the embodiment of FIGS. 11A-B, the necessary quantity of electrodes 30 for the desired test is prepackaged in separate sections 92 of distinct plastic elec-
trde trays 94 of an electrode storage system 96. In this example, three distinct tray sections 92 each hold twenty electrodes 30 (for a typical EEG test), and ten trays 94 are shown stacked and readily accessible upon one another for ease of storage, delivery, transport, etc. When the associated headset 12 needs to be fitted with a set of electrodes 30, a tray 94 is uncovered (e.g. by removal of a cover 95 or an upper tray 94) and the electrically-conductive liquid 90 is squirited, sprayed or poured onto the electrodes 30 in a first tray section 92, preserving the dry status of the other electrodes 30 in the tray 94 and storage system 96 for future use.

Referring to FIGS. 1-5, the electrically-conductive liquid laden electrodes 30 may then be inserted onto the headset 12 (see also, FIGS. 12-19C). The exemplary headset system 10 may then be placed and/or fitted on the subject's head 98 so that each (electrically-conductive liquid laden) electrode 30 is positioned to contact the scalp 102 as desired. However, if the contact between any electrode 30 is not satisfactory or for any other suitable reason, the administrator of the test may add additional electrically-conductive liquid 90 between the electrode 30 and the scalp 102. For example, additional electrically-conductive liquid 90 containing optical/contact lens solution may be inserted between the elec-
trode 30 and scalp 102, such as with a squirt bottle, blunt needle, plastic syringe or other applicator. For another example, electrically-conductive liquid 90 containing hair conditioner may be inserted between the electrode 30 and scalp 102, such as with a squirt bottle, tube, blunt needle, plastic syringe or other applicator.

In some scenarios, electrically-conductive liquid 90 in the form of both the optical/contact lens solution and hair conditioner may be added between an electrode 30 and the scalp 102. For example, if the optical/contact lens solution is added and does not sufficiently enhance the desired electric conductivity, hair conditioner may then be added. For another example, if it is desirable to avoid dripping of the electrically-conductive liquid 90 at or around a particular electrode site, the hair conditioner (or an electrically-conductive liquid 90 with a mixture of ingredients that includes hair conditioner) may be preferred. It may be desirable to avoid dripping of the electrically-conductive liquid 90, for example, at electrode sites at locations that may be more prone to dripping, such as along the side of the subject's head 98. For example, if added electrically-conduc-
tive liquid 90 would be likely drip onto an area of the scalp 102 between adjacent electrodes 30, the dripped electrically-conductive liquid 90 could cause the signal measure-
ments of adjacent electrodes 30 to be distorted. At such electrode sites, it may thus be desirable to use the hair conditioner as the (added) electrically-conductive liquid 90 because it is less likely to drip.

In some scenarios, the subject may have a preference as to which electrically-conductive liquid 90 to use on their head 98. For example, subject's having hair that has been straightened may have a heightened desire to wet their hair because wetting may reverse or remove the straighten-
ing. In such instances, the subject may prefer the use of the hair conditioner-type electrically-conductive liquid 90 to preserve the straightening of their hair. Another example is a situation where it may be preferred to add the hair conditioner instead of optical/contact lens solution is when the viscosity or thickness of the electrically-conductive liquid 90 is important. This may be the case, for example, when the headset 12 is placed or fitted onto the subject's head 98 and a gap exists between one or more of the electrodes 30 and the scalp 102. For example, the subject's hair style (e.g. corcurrent) may not allow an electrode 30 to get close enough to the scalp 102 to sufficiently receive signals from the subject's brain. In such instance, the thickness or viscosity of the hair conditioner may fill the gap between the electrode 30 and scalp 102 sufficient to provide acceptable conduc-
tivity between the head and the electrode 30. In some embodiments, the electrodes 30 (laden with electrically-conductive liquid) may be first positioned in the headset 12 in a retracted position. Thereafter, the headset 12 may be fitted onto the subject's head 98 without dripping the electrically-conductive liquid all over the head 98. In some instances, good contact is made with the scalp 102 and the signal transmission path from the scalp 102 to the electrode 30 is acceptable. However, after the test is initi-
ated, if the electrical impedance or conductivity is insuffi-
cient, additional electrically-conductive liquid 90 (e.g., optical/contact lens solution, hair conditioner or a combination thereof) may be added as needed.

In various embodiments, the present disclosure may include any of the features mentioned above and/or one or more of the following features: a lightweight headset system 10 that adjusts conformance to a wide range of head sizes and shapes; a headset system 10 having electrodes 30 that may be independently inserted and adjusted for one or more purposes, such as to make adjustments or changes to improve electrical conductivity and signal transmission (e.g., accommodate a wide range of hair types, skin dryness, patient sensitivities to pressure, etc.); a headset system 10 that may be inexpensively reused and shared with multiple patients with less risk of transfer dirt, oil, germs, etc.; electrodes 30 that are replaceable, and may be replaced with another style, size or configuration electrode 30; an electrically-conductive liquid 90 useful between the elec-

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trodcs 30 and the subject's head 98 may be used to provide sufficient electrical conductivity for subjects with different hair styles and conditions, does not require washing or cleaning the hair and scalp after the test or any combination thereof; or a combination thereof.

Preferred embodiments of the present disclosure thus offer advantages over the prior art and are well adapted to carry out one or more of the objects of this disclosure. However, the claimed invention of any particular claim(s) does not require each of the components and acts described above and is in no way limited to the above-described embodiments or methods of operation, except and only to the extent as may be explicitly recited in one or more of the appended claims and only for those claims and any claims depending therefrom. Any one or more of the above components, features and processes may be employed in any suitable configuration, including one or more of other similar components, features and processes. Moreover, the present invention includes additional features, capabilities, functions, methods, uses and applications that have not been specifically addressed herein but are, or will become, apparent from the description herein, the appended drawings and claims. All structural and functional equivalents to components of the above-described embodiments and additional embodiments as regarded by those of ordinary skill in the art are hereby expressly incorporated by reference and are intended to be encompassed by the present claims.

The methods that may be described above or claimed herein and any other methods which may fall within the scope of the appended claims may be performed in any desired suitable order and are not necessarily limited to any sequence described herein or as may be listed in the appended claims. Further, the methods of the present invention do not necessarily require use of the particular embodiments shown and described herein, but are equally applicable with any other suitable structure, form and configuration of components.

While exemplary embodiments of the invention have been shown and described, many variations, modifications and/or changes of the system, apparatus and methods of the present invention, such as in the components, details of construction and operation, arrangement of parts and/or methods of use, are possible, contemplated by the patent applicant(s), within the scope of the appended claims, and may be made and used by one of ordinary skill in the art without departing from the spirit of the invention and scope of appended claims. Thus, all matter herein set forth or shown in the accompanying drawings should be interpreted as illustrative, and the scope of the disclosure and the appended claims should not be limited to the embodiments described and shown herein. Furthermore, no component, method step or detail thereof made or shown in the present disclosure is intended to be dedicated to the public regardless of whether it is explicitly recited in the claims. In addition, the various changes and modifications in form, material and other details of the disclosed embodiments as may be apparent to those of ordinary skill in the art without departing from the spirit and scope of the present disclosure are also encompassed by the present disclosure.

The invention claimed is:

1. Apparatus for use in connection with receiving electroencephalographic (EEG) signals from a human subject's head through the scalp, said apparatus comprising: a removable headset arranged and adapted to extend at least partially around the subject's head over at least part of the subject's scalp, said headset including an inner side and an outer side, said inner side being closest to the subject's scalp when said headset is positioned least partially around the subject's head; and said headset further including a plurality of electrode stations and a plurality of intermediate portions extending between said electrode stations and shaped and sized to form open spaces therebetween, each said electrode station having an electrode aperture extending therefrom to said outer side of said headset and partially oriented thereon, each said electrode aperture including a plurality of non-conductive biasing flaps, said biasing flap being coupled to said headset and at least partially oriented over said electrode apertures, said headset further including at least one EEG signal transmission wire associated with said electrode stations for receiving EEG signals; a plurality of removable electrodes releasably engageable with said headset and useful to facilitate the transmission of EEG signals from the subject's head to at least one said EEG signal transmission wire of said headset during use of said headset, each said electrode being positioned at an end, bottom end and at least one side extending therebetween, wherein each said electrode is configured to be releasably suspended within one of said electrode apertures and biased between said headset and the subject's head by said associated biasing flap; and a plurality of electrode covers constructed at least partially of flexible, liquid-absorbing material and arranged and adapted to be electrically-conductive, electrically-conductive ring disposed within each said electrode aperture, constructed at least partially of electrically-conductive material and electrically coupled to at least one said EEG signal transmission wire of said headset; wherein during use of said headset, each said electrically-conductive ring is arranged and adapted to receive EEG signals from said associated electrode cover and transmit such signals to said at least one said EEG signal transmission wire of said headset.

2. The apparatus of claim 1 further including an electrically-conductive ring disposed within each said electrode aperture, constructed at least partially of electrically-conductive material and electrically coupled to at least one said EEG signal transmission wire of said headset, wherein during use of said headset, each said electrically-conductive ring is arranged and adapted to receive EEG signals from said associated electrode cover and transmit such signals to said at least one said EEG signal transmission wire of said headset.

3. The apparatus of claim 2 wherein each said electrode cover includes a side surface and a bottom end that is electrically-conductive to said side surface, wherein said bottom end of each said electrode cover is arranged and adapted to electrically-conductively engage the subject's head to receive EEG signals therefrom and said side surface of each said electrode cover is arranged and adapted to electrically-conductively engage said associated electrically-conductive ring to transmit the EEG signals received from the subject's head to said electrically-conductive ring during use of said headset.

4. The apparatus of claim 1 wherein each said electrode cover includes a bottom end, said bottom end of each said electrode cover being configured to be removably and slideably engage each associated biasing flap disposed by said headset.

5. The apparatus of claim 1 wherein each said electrode cover is configured at least partially of at least one among
the group consisting of natural fabric, natural fibers, synthetic fabric, synthetic fibers and exfoliating material.

6. The apparatus of claim 1 wherein each said electrode cover is constructed and configured to provide sufficient surface contact with the subject’s scalp during use of the headset to receive acceptable EEG signals from the subject’s head.

7. The apparatus of claim 1 wherein each said electrode cover is configured to contact the subject’s head at a contact interface during use of said headset, further wherein said intermediate portions of said headset and said open spaces therebetween are arranged and adapted to allow said contact interfaces to be viewable by the naked eye during use of said headset.

8. The apparatus of claim 7 wherein said intermediate portions of said headset are configured to flex to assist in conforming said headset to the shape of the subject’s head and allow said contact interfaces to be viewable by the naked eye during use of said headset.

9. The apparatus of claim 1 wherein each said electrode is a unitary member entirely encapsulated by its said associated electrode cover to form an electrode-cover combination, further wherein each said electrode-cover combination is disposable.

10. The apparatus of claim 1 wherein said electrically-conductive liquid includes at least one among the group consisting of hair conditioner and optical contact lens solution.

11. The apparatus of claim 1 wherein said intermediate portions of said headset include at least one among the group consisting of rubber, foam rubber, silicon, closed-cell resin material, closed-cell copolymer, material, biostatic material and antiaerosol material.

12. The apparatus of claim 1 wherein at least some of said intermediate portions of said headset include at least one among the group consisting of rubber, foam rubber, silicon, closed-cell resin material, closed-cell copolymer, material, biostatic material and antiaerosol material.

13. The apparatus of claim 1 wherein each said biasing flap is constructed at least partially of resilient material, further including first and second flap fasteners associated with each said biasing flap and adapted to releasably secure said associated biasing flap to said headset on opposite sides of said associated electrode aperture.

14. The apparatus of claim 1 wherein each said electrode includes at least one protrusion extending outwardly from at least one said side of said associated electrode, said protrusion being arranged and adapted to selectively position said electrode relative to said associated electrode aperture.

15. The apparatus of claim 14 wherein each said electrode has a cylindrical shape, further wherein said at least one protrusion comprises a circular ridge extending at least partially around the outer circumference of said associated electrode, further wherein said electrode cover is configured to conform to the shape of said at least one protrusion of said associated electrode.

16. The apparatus of claim 14 further including an electrode retention ring disposed within at least one among the group consisting of said electrode aperture and said biasing flap associated with said electrode station, each said electrode retention ring having an upper edge facing said outer side of said headset and a lower edge facing said inner side of said headset.

17. The apparatus of claim 16 wherein each said biasing flap includes a flap hole at least partially aligned over said associated electrode aperture, further wherein each said associated electrode retention ring is disposed within said flap hole of said associated biasing flap, further wherein each said electrode retention ring includes at least one groove configured to selectively retain said at least one protrusion of said associated electrode, whereby when said at least one protrusion is selectively secured in said groove of said associated biasing flap, said electrode is configured to be moveable with said biasing flap relative to said electrode aperture and the subject’s head during use of said headset.

18. The apparatus of claim 17 further including a plurality of electrically-conductive rings, one of said electrically-conductive rings being disposed within each said electrode aperture, each said electrically-conductive ring being electrically coupled to at least one said EEG signal transmission wire of said headset and wherein during use of said headset, each said electrode retention ring is arranged and adapted to receive EEG signals from said associated electrode cover to said at least one EEG signal transmission wire.

19. The apparatus of claim 16 wherein each said biasing flap is coupled to said outer side of said headset over said associated electrode aperture and configured to allow said biasing force to said top end of said associated electrode.

20. The apparatus of claim 16 wherein one of said electrode retention rings is disposed within each said electrode aperture, constructed at least partially of electrically-conductive material, electrically coupled to at least one said EEG signal transmission wire of said headset, further wherein each said electrode is movable relative to said headset between at least one retracted position and at least one extended position, each said electrode in said retracted and extended positions being biased by said associated biasing flap in the direction of the subject’s head during use of said headset, wherein when any said electrode is in at least one said retracted position, said at least one protrusion of said electrode is positioned closer to said upper edge of said retention ring than said lower edge of said retention ring, and when any said electrode is to said at least one extended position, said at least one protrusion of said electrode is positioned closer to said lower edge of said retention ring than said upper edge of said retention ring.

21. The apparatus of claim 20 wherein each said electrode is configured to be moveable within a distinct range of said retracted positions and a distinct range of said extended positions.

22. The apparatus of claim 1 wherein each said biasing flap includes a flap hole at least partially aligned over said associated electrode aperture, further wherein each said electrode is sized and configured to be releasably engaged with said headset by insertion one of said said flap holes and said associated electrode aperture from said outer side of said headset and removed from said headset by being moved through said associated flap hole and said associated electrode aperture in the direction of said inner side of said headset.

23. The method comprising: releasably suspending the plurality of electrodes along with their associated electrically-conductive, liquid
laden, electrode covers within the respective associated electrode apertures in the headset; placing the headset on the subject's head;

at least some of the biasing flaps biasing their associated electrodes in the direction of the subject's head independent of the other electrodes in the headset; and at least some of the electrode covers receiving useful signals from the subject's head and transmitting the received signals to at least one EEG signal transmission wire in the headset.

25. The method of claim 24 wherein each electrode is moveable between at least one retracted position and at least one extended position, the top end of each electrode in an extended position being closer to the outer side of the headset than the position of the top end of the electrode relative to the outer side of the headset in a retracted position, further including selectively, independently positioning each electrode in at least one retracted position, and if any of the respective electrode covers is not receiving useful signals from the subject's head, selectively, independently moving each such electrode from at least one retracted position to at least one extended position.

26. Apparatus for use in connection with receiving electroencephalographic (EEG) signals from a human subject's head through the scalp thereof, the apparatus comprising: a removable headset arranged and adapted to extend at least partially around the subject's head over at least part of the subject's scalp, said headset including an inner side and an outer side, said inner side being closest to the subject's scalp when said headset is positioned least partially around the subject's head, said headset further including a plurality of electrode stations and a plurality of intermediate portions extending between said electrode stations and shaped and sized to form open spaces therebetween, each said electrode station having an electrode aperture extending therethrough from said outer side to said inner side of said headset, said headset further including a plurality of non-conductive biasing flaps, each said biasing flap being combined to said headset and at least partially aligned over one of said electrode apertures, said headset further including at least one EEG signal transmission wire associated with said electrode stations for receiving EEG signals; and a plurality of removable electrodes releasably engageable with said headset and useful to facilitate the transmission of EEG signals from the subject's head to at least one said EEG signal transmission wire of said headset during use of said headset, each said electrode including a top end, bottom end, at least one side extending therebetween and at least one protrusion extending outwardly from said least one side, said protrusion being arranged and adapted selectively to position said associated electrode relative to said associated electrode aperture, wherein each said electrode is configured to be releasably suspended within one of said electrode apertures and biased towards the subject's head by said associated biasing flap.

27. The apparatus of claim 26 wherein each said biasing flap includes a flap hole at least partially aligned over said associated electrode aperture, further wherein each said flap hole includes at least one groove configured to selectively remid said at least one protrusion of said associated electrode, whereby when said at least one protrusion is selectively secured in said groove of said associated biasing flap, said electrode is configured to be moveable with said biasing flap relative to said electrode aperture during use of said headset.

28. The apparatus of claim 27 wherein each said electrode is sized and configured to be releasably engaged with said headset by insertion into one of said flap holes and said associated electrode aperture from said outer side of said headset and removed from said headset by being moved through said associated flap hole and said associated electrode aperture in the direction of said inner side of said headset.

29. The apparatus of claim 26 wherein each said biasing flap is coupled to said outer side of said headset over said associated electrode aperture and configured to abut and apply biasing forces to said top end of said associated electrode, further wherein each said electrode is moveable relative to said headset between at least one retracted position and at least one extended position, each said electrode in said retracted and extended positions being biased by said associated biasing flap in the direction of the subject's head during use of said headset, wherein when any said electrode is in at least one said retracted position, said at least one protrusion of said electrode is positioned closer to said outer side of said headset than said inner side of said headset, and when any said electrode is in at least one extended position, said at least one protrusion of said electrode is positioned closer to said inner side of said headset than said outer side of said headset.

30. The apparatus of claim 29 wherein each said electrode is configured to be moveable within a distinct range of said retracted positions and a distinct range of said extended positions.

31. The apparatus of claim 26 further including an electrode retention ring disposed within at least one among the group consisting of said electrode aperture and said biasing flap associated with each said electrode station, each said electrode retention ring having an upper edge facing said outer side of said headset and a lower edge facing said inner side of said headset, further wherein each said electrode is moveable relative to said headset between at least one retracted position and at least one extended position, each said electrode in said retracted and extended positions being biased by said associated biasing flap in the direction of the subject's head during use of said headset, wherein when any said electrode is in at least one said retracted position, said at least one protrusion of said electrode is positioned closer to said upper edge of said retention ring, and when any said electrode is in said at least one extended position, said at least one protrusion of said electrode is positioned closer to said lower edge of said retention ring than said upper edge of said retention ring.

32. The apparatus of claim 26 further including a plurality of electrode covers constructed at least partially of flexible, liquid-absorbing material and arranged and adapted to be electrically-conductive, receive EEG signals from the subject's head and transmit such signals to at least one said EEG signal transmission wire of said headset during use of said headset, each said electrode cover at least partially encapsulating said electrode and being laden with electrically-conductive liquid in use of said headset, wherein said each biasing flap is configured to bias said associated electrode cover into contact with the subject's head to allow said associated cover to receive EEG signals from the subject's head.

33. The apparatus of claim 32 further including an electrically-conductive ring disposed within each said electrode aperture, constructed at least partially of electrically-conductive material.
ductive material and electrically coupled to at least one said EEG signal transmission wire of said headset, wherein during use of said headset, each said electrically-conductive ring is arranged and adapted to receive EEG signals from said associated electrode cover and transmit such signals to said at least one said EEG signal transmission wire of said headset.

34. The apparatus of claim 32 wherein each said electrode has a cylindrical shape, further wherein said first electrode comprises a circular ridge extending at least partially around the outer circumference of said associated electrode, further wherein said electrode cover is configured to conform to the shape of said at least one promontion of said associated electrode.

35. A method of using the apparatus of claim 26, the method comprising:
releasably suspending the plurality of electrodes within the respective associated electrode apertures in the headset;
- placing the headset on the subject's head; and
- at least some of the biasing flaps biasing their associated electrodes in the direction of the subject's head independent of the other electrodes in the headset.

36. Apparatus for use in connection with receiving electroencephalographic (EEG) signals from a human subject's head through the scalp thereof, the apparatus comprising:
a removable headset arranged and adapted to extend at least partially around the subject's head over at least part of the subject's scalp, said headset including an inner side and an outer side, said inner side being closest to the subject's scalp when said headset is positioned least partially around the subject's head, said headset further including a plurality of electrode stations and a plurality of intermediate portions extending between said electrode stations and shaped and sized to form open spaces therebetween, said electrode station having an electrode aperture extending therethrough from said outer side to said inner side of said headset, said headset further including a plurality of biasing flaps, each said biasing flap being coupled to said headset and at least partially aligned over one of said electrode apertures, said headset further including at least one EEG signal transmission wire associated with said electrode stations for receiving EEG signals; and
- a plurality of removable electrodes releasably engageable with said headset and useful to facilitate the transmission of EEG signals from the subject's head to at least one said EEG signal transmission wire of said headset during use of said headset, each said electrode including a top end, bottom end, at least one side extending therefrom and at least one protrusion extending outwardly from said at least one side, said protrusion being arranged and adapted to selectively position said associated electrode relative to said associated electrode aperture, wherein said electrode is configured to be releasably suspended within one of said electrode apertures and biased towards the subject's head by said associated biasing flap, further wherein each said biasing flap includes a flabe portion that is a projection of said associated electrode, whereby when at least one protrusion is selectively secured in said groove of said associated biasing flap, said electrode is configured to be moveable with said biasing flap relative to said electrode aperture during use of said headset.

37. Apparatus for use in connection with receiving electroencephalographic (EEG) signals from a human subject's head through the scalp thereof, the apparatus comprising:
a removable headset arranged and adapted to extend at least partially around the subject's head over at least part of the subject's scalp, said headset including an inner side and an outer side, said inner side being closest to the subject's scalp when said headset is positioned least partially around the subject's head, said headset further including a plurality of electrode stations and a plurality of intermediate portions extending between said electrode stations and shaped and sized to form open spaces therebetween, each said electrode station having an electrode aperture extending therefrom from said outer side to said inner side of said headset, said headset further including at least one EEG signal transmission wire associated with said electrode stations for receiving EEG signals; a plurality of removable electrodes releasably engageable with said headset and useful to facilitate the transmission of EEG signals from the subject's head to at least one said EEG signal transmission wire of said headset during use of said headset, each said electrode including a top end, bottom end and at least one side extending therefrom, wherein each said electrode is configured to be releasably suspended within one of said electrode apertures and biased between said headset and the subject's head by said associated biasing flap; and
- a plurality of electrode covers constructed at least partially of flexible, liquid-absorbing material and arranged and adapted to be electrically-conductive, receive EEG signals from the subject's head and transmit such signals to at least one said EEG signal transmission wire of said headset during use of said headset, each said electrode cover at least partially encapsulating said electrode and being disposed with electrically-conductive liquid during use of said headset, wherein said biasing flap is configured to bias said associated electrode cover into contact with the subject's head to allow said associated cover to receive EEG signals from the subject's head.

38. The apparatus of claim 37 further including an electrically-conductive ring disposed within each said electrode aperture, constructed at least partially of electrically-conductive material and electrically coupled to at least one said EEG signal transmission wire of said headset, wherein during use of said headset, each said electrically-conductive ring is arranged and adapted to receive EEG signals from said associated electrode cover and transmit such signals to said at least one said EEG signal transmission wire of said headset.

39. The apparatus of claim 37 wherein each said electrode is a unitary member entirely encapsulated by its said associated electrode cover to form an electrode-cover combination, further wherein each said electrode-cover combination is disposable.

40. The apparatus of claim 37 wherein each said electrode includes at least one protrusion extending outwardly from at least one said side of said associated electrode, said protru-
Apparatus for use in connection with receiving electroencephalographic (EEG) signals from a human subject's head through the scalp thereof, the apparatus comprising:

- a removable headband arranged and adapted to extend at least partially around the subject's head and at least partially including the subject's scalp, said headband including an inner side and an outer side, said inner side being contiguous to the subject's scalp when said headband is positioned at least partially around the subject's head, said headband further including a plurality of electrode stations and a plurality of intermediate portions extending between said electrode stations and shaped and sized to form open spaces therebetween, each said electrode station having an electrode aperture extending therethrough from said outer side to said inner side of said headband, said headband further including a plurality of biasing flaps and at least first and second biasing flaps associated with each said biasing flap, each said biasing flap being coupled to said headband and at least partially aligned over one of said electrode apertures, said at least first and second biasing flaps being adapted to secure said associated biasing flap to said headband on opposite sides of said associated electrode aperture, said headband further including at least one EEG signal transmission wire associated with said electrode station for receiving EEG signals, a plurality of removable electrodes releasably engageable with said headband and useful to facilitate the transmission of EEG signals from the subject's head to at least one said EEG signal transmission wire of said headband during use of said headband, each said electrode including a top end, a bottom end and at least one side extending therebetween, wherein each said electrode is configured to be releasably suspended within one of said electrode apertures and biased between said headband and the subject's head by said associated biasing flap; and

- a plurality of electrode covers constructed at least partially of flexible, liquid-absorbing material and arranged and adapted to be electrically-conductive, receive EEG signals from the subject's head and transmit such signals to at least one said EEG signal transmission wire of said headband during use of said headband, each said electrode cover at least partially encapsulating said said electrode and being laden with electrically-conductive liquid during use of said headband, wherein said said biasing flap is configured to bias said associated electrode cover into contact with the subject's head to allow said associated cover to receive EEG signals from the subject's head.

The apparatus of claim 47 further including an electrically-conductive ring disposed within each said electrode aperture, constructed at least partially of electrically-conductive material and electrically coupled to at least one said EEG signal transmission wire of said headband, wherein during use of said headband, each said electrically-conductive ring is arranged and adapted to receive EEG signals from said said associated electrode cover and transmit such signals to said at least one said EEG signal transmission wire of said headband.

A method of using the apparatus of claim 47, the method comprising:

- releasably suspending the plurality of electrodes along with their associated electrically-conductive, liquid laden, electrode covers within the respective associated electrode apertures in the headband, placing the headband on the subject's head; at least some of the biasing flaps biasing their associated electrodes in the direction of the subject's head independent of the other electrodes in the headband; and at least some of the electrode covers receiving useful signals from the subject's head and transmitting the received signals to at least one EEG signal transmission wire in the headband.
liquid-absorbing material and arranged and adapted to be electrically-conductive, receive EEG signals from the subject's head and transmit such signals to at least one said EEG signal transmission wire of said headset during use of said headset, each said electrode cover at least partially encompassing one said electrode and being laden with electrically-conductive liquid during use of said headset, wherein said each biasing flap is configured to bias said associated electrode cover into contact with the subject's head to allow said associated cover to receive EEG signals from the subject's head.

53. The apparatus of claim 52 further including an electrically-conductive ring disposed within each said electrode aperture, constructed at least partially of electrically-conductive material and electrically coupled to at least one said EEG signal transmission wire of said headset, said electrically-conductive ring being arranged and adapted to receive EEG signals from said associated electrode aperture and transmit said EEG signal transmission wire of said headset.

54. A method of using the apparatus of claim 50, the method comprising: releasably suspending the plurality of electrodes within the respective associated electrode apertures in the headset; placing the headset on the subject's head; and at least some of the biasing flaps biasing their associated electrodes in the direction of the subject's head independent of the other electrodes in the headset.

55. Apparatus for use in connection with receiving electroencephalographic (EEG) signals from a human subject's head through the scalp thereof, the apparatus comprising: a removable headset arranged and adapted to extend at least partially around the subject's head over at least part of the subject's scalp to which said headset is secured; said headset including an inner side and an outer side, said inner side being closest to the subject's scalp when said headset is secured and an aperture therein including a plurality of electrode stations and a plurality of intermediate portions extending between said electrode stations and shaped and sized to form open spaces therebetween, each said electrode station having an electrode aperture extending therethrough from said outer side to said inner side of said headset, said headset further including an plurality of biasing flaps, each said biasing flap being releasably suspended over one of said said electrode apertures, said headset further including at least one EEG signal transmission wire associated with said electrode stations for receiving EEG signals and a plurality of removable electrodes releasably engageable with said headset and useful to facilitate the transmission of EEG signals from the subject's head to at least one said EEG signal transmission wire of said headset during use of said headset, each said electrode including a top end, bottom end, at least one side extending therebetween and at least one protrusion extending outwardly from said at least one side, said protrusion being releasably suspended within one of said electrode apertures and biased towards the subject's head by said associated biasing flap.

51. The apparatus of claim 50 further including an electrode retention ring disposed within at least one among the group consisting of said electrode aperture and said biasing flap associated with each said electrode station, each said electrode retention ring having an upper edge facing said outer side of said headset and a lower edge facing said inner side of said headset, further wherein said each said electrode is movable relative to said headset between at least one retracted position and at least one extended position, each said electrode in said retracted and extended positions being biased by said associated biasing flap in the direction of the subject's head during use of said headset, wherein when any said electrode is in at least one said retracted position, said at least one protrusion of said electrode is positioned closer to said upper edge of said retention ring than said lower edge of said retention ring, and when any said electrode is in at least one said extended position, said at least one protrusion of said electrode is positioned closer to said lower edge of said retention ring than said upper edge of said retention ring.

52. The apparatus of claim 50 further including a plurality of electrode covers constructed at least partially of flexible,
trode aperture, wherein each said electrode is configured to be releasably suspended within one of said electrode apertures and biased towards the subject's head by said associated biasing flap.

56. The apparatus of claim 55 further including an electrode retention ring disposed within at least one among the group consisting of said electrode aperture and said biasing flap associated with each said electrode station, each said electrode retention ring having an upper edge facing said outer side of said headset and a lower edge facing said inner side of said headset, further wherein each said electrode is movable relative to said headset between at least one retracted position and at least one extended position, each said electrode in said retracted and extended positions being biased by said associated biasing flap in the direction of the subject's head during use of said headset, wherein when any said electrode is in at least one said retracted position, said at least one protrusion of said electrode is positioned closer to said upper edge of said retention ring than said lower edge of said retention ring, and when any said electrode is in said at least one extended position, said at least one protrusion of said electrode is positioned closer to said lower edge of said retention ring than said upper edge of said retention ring.

57. The apparatus of claim 55 further including a plurality of electrode covers constructed at least partially of flexible, liquid-absorbing material and arranged and adapted to be electrically-conductive, receive EEG signals from the subject's head and transmit such signals to at least one said EEG signal transmission wire of said headset during use of said headset, each said electrode cover at least partially encased in said associated electrode cover into contact with the subject's head to allow said associated cover to receive EEG signals from the subject's head.

58. The apparatus of claim 57 further including an electrically-conductive ring disposed within each said electrode aperture, constructed at least partially of electrically-conductive material and electrically coupled to at least one said EEG signal transmission wire of said headset, wherein during use of said headset, each said electrically-conductive ring is arranged and adapted to receive EEG signals from said associated electrode cover and transmit such signals to said at least one said EEG signal transmission wire of said headset.

59. A method of using the apparatus of claim 55, the method comprising:

- releasably suspending the plurality of electrodes within the respective associated electrode apertures in the headset;
- placing the headset on the subject's head; and
- at least some of the biasing flaps biasing their associated electrodes in the direction of the subject's head independent of the other electrodes in the headset.

* * * * *
Indications for Use

BE SURE TO READ THE ENTIRE WAVI INSTRUCTION MANUAL BEFORE USING THE WAVI HEADSET OR WAVI DESKTOP SOFTWARE. THIS MANUAL IS FOR RESEARCH PURPOSES ONLY.

The WAVI Desktop software is provided as a service for use in collaborative clinical and research settings where a combination of research-EEG with evoked responses and public domain assessment tools is desired.

Disclaimer:
WAVI reports have not been evaluated by the FDA and are provided for research, education, and information. WAVI makes no warranty as to the accuracy of the screening and assessment tools.

Issuance Date: 02-2020
Revision: 0.9.8.17

For additional information on the WAVI Headset, please visit our website at www.wavimed.com.

The WAVI Headset labeling and instructions for use manual are consistent with FDA regulation requirements listed in section 801.

Contraindications
There are no known contraindications to the use of this device.
This device is non-sterile and does not require sterilization prior to use.

Cautionary Statements
- Do not use the WAVI headset on or near open wounds. Do not use the WAVI headset on or near skin that is bruised or weakened due to either injury or the medical condition of the patient.
- Instruct patients to communicate any persistent redness, soreness or swelling at the area of the scalp corresponding with electrode locations.
- It is not recommended that the headset be left in place for longer than any single recording session.
- Avoid eye contact with solutions as it may cause mild transient irritation. Wash eyes with appropriate 0.9% saline solution, commercial eye wash solution or water to flush out residual particles. Avoid rubbing eyes.
- All WAVI products should be stored at room temperature with the container, package or box closed or sealed.
- The WAVI headset is for external use only.
- The WAVI headset is not designed for nor should ever be used for any type of stimulation.
- Keep out of the reach of children.

No adverse reactions or medical complications related to the use of this device were reported.

Paul Mitchell: The Cream® is a registered trademark of John Paul Mitchell Systems ©

NuPrep® is a registered trademark of Weaver and Company ©

Boa Fit System® and Boa® are registered trademarks of Boa Technology Inc ©
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HEADSETS
(1) Small Headset
(1) Medium Headset
(1) Large Headset
(Extra Large Headsets are available by special order)

SOLUTIONS
(1) 25g bottle of NuPrep® Skin Prep Gel or WAVi approved solution
(1) Paul Mitchell® The Cream Styling Conditioner or WAVi approved solution
(3) Bottles 100 mL 0.9% Sodium Chloride Saline Solution

ELECTRONICS
(1) Laptop PC with WAVi Desktop software
(1) Laptop PC Charger
(1) USB Mouse
(1) WAVi Electronic Processing Unit (EPU)
(1) USB Mini-B cable for EPU
(1) Headphones
(1) 3.5mm auxiliary cable for headphones

ACCESSORIES
(1) WAVi Portable Bag
(2) Headset Racks
(10) WAVi eSoc™ Trays (6 scans)
(10) Extended WAVi eSacs™
(1) WAVi Sizing Ribbon
(3) Syringes
(5) Blunt Needles
(1) WAVi Towel
(2) Magnetic Ear Electrodes
(6) Alcohol Prep Pads
(6) Diamond Bands

DOCUMENTATION
(1) WAVi Instruction Manual
(1) WAVi Quick Setup and Scan Guide
(1) WAVi Cloud Instruction Manual
2 WAVi Sessions

A. Equipment Setup

In preparation for the scan, arrange all parts and accessories on a table (Figure 2.11).

Fill one blunt needle syringe with saline solution and one with electro-conductive cream such as Paul Mitchell The Cream or another WAVi approved solution (Figure 2.12).

B. WAVi eSoc™ Electrode Contact Preparation

Remove one compartment lid from the tray of WAVi eSoc single use electrodes. Pour 25mL of 0.9% sodium chloride saline solution evenly over all 20 eSocs (Figure 2.21). Allow eSocs to soak while continuing with the setup process. Make sure to squeeze or wipe some of the liquid off of the eSocs before inserting them into the WAVi Headset. Excess dripping liquid can damage the electronic components.

Note: Do not soak eSocs with water or any liquid other than 0.9% sodium chloride saline solution.
C. Laptop Preparation

After signing into the laptop, make sure it is in **airplane mode** before opening the WAVi Desktop software. To check if airplane mode is active, look for an airplane icon in the bottom right corner of the screen. If you see a Wi-Fi icon instead of an airplane icon, click the Wi-Fi icon and select airplane mode “On” (Figure 2.3.1).

Plug the mouse into a laptop USB port on the side of the participant’s preferred hand.

Plug one end of the USB Mini-B cable into the bottom of the EPU (Figure 2.3.2) and the other end into any available USB port on the laptop. Allow the EPU time to initialize.

After plugging in the EPU, a Windows device setup bar may briefly appear at the bottom of the screen. If this happens, allow the bar to disappear before opening the **WAVi Desktop** software.

To open the **WAVi Desktop** software, double click the **WAVi Desktop icon** (Figure 2.3.3).

After the app starts up, the welcome screen is shown (Figure 2.3.4).

For new participants, press the **Create New Profile** button. Otherwise, press the **Manage Profiles** button and then navigate to the participant’s existing profile.

If creating a new profile, input basic information for the new participant (Figure 2.3.5). You are not required to fill out all fields, but you must provide at least a birthdate. It is also recommended to provide at least a first and/or last name. When finished, press **Save**.
If this is a new profile, a popup will appear requesting the participant to add a consent form. Choose Yes (Figure 2.3.6), then select WAVi IRB Consent Form in the dialog window (Figure 2.3.7).

(The consent form may also be added later by selecting +New Document from the Documents tab.)

Instruct participant and/or their guardian to read and complete the WAVi IRB Consent Form, using the touch screen to sign. Click Exit Form in the upper right corner when complete. The information entered on the form will be automatically saved to the profile.

D. Participant Preparation

Have the participant remove any bobby pins, barrettes, ponytails, and earrings. Only the earrings on the earlobes need to be removed. Cartilage piercings and other piercings do not need to be removed.

Make sure the participant turns off their cell phone(s) to avoid any distractions or electrical interference during testing.
E. Headset Preparation

Measure the circumference of the participant’s head using the WAVi sizing ribbon. Hold the arrow on the sizing ribbon one inch above the nasion (the most indented point on the bridge of the nose) and wrap the other end of the ribbon around the head, passing one inch above the inion (the boney protuberance at the base of the skull). Use the headset size indicators on the sizing ribbon to determine which headset size will fit best (Figure 2.5.1).

Note: When measuring children, place the sizing ribbon about 1/2 inch lower.

The headset size is indicated on the inside of the flap at the back of the headset (Figure 2.5.2). Headsets are available in Small, Medium, and Large sizes. Extra Large headsets are available by special order.

<table>
<thead>
<tr>
<th>The various headsets fit the following head sizes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra Large (XL)</td>
</tr>
<tr>
<td>Large (L)</td>
</tr>
<tr>
<td>Medium (M)</td>
</tr>
<tr>
<td>Small (S)</td>
</tr>
<tr>
<td>fits 62-66cm head circumference</td>
</tr>
<tr>
<td>fits 58-62cm head circumference</td>
</tr>
<tr>
<td>fits 54-58cm head circumference</td>
</tr>
<tr>
<td>fits 50-54cm head circumference</td>
</tr>
</tbody>
</table>

The WAVi Headset has 19 recording channels which are named according to the International 10-20 EEG naming conventions (Figure 2.5.4), a ground location (G), and two reference channels (A1 and A2).
Place all 20 soaked eSocs into the metal electrode rings on the headset (Figure 2.5.5). Make sure the blue ends are facing the diamond bands and the white ends are facing the scalp. Find the two prongs at the bottom of the eSoc. Squeeze the prongs together to allow them to snap into position in the metal electrode rings. The order in which the eSocs are placed into the headset is not important. Make sure that all 20 eSocs are securely inserted into the metal electrode rings.

Ensure the headset is centered on the participant’s head by aligning the front gap with the center of the nose.

Align the U-shaped hole at the back of the headset with the inion (Figure 2.5.7, inion displayed in Figure 2.5.8).

After the headset is centered and firmly secured on the participant’s head, use the blunt needle syringe to add electro-conductive cream to the ground (G) (Figure 2.5.8). Place a pea-sized drop in between the white tip of the eSoc and the scalp. This helps to achieve a good ground contact, which is critical to obtaining clean data when running a scan.
Place a pea size amount of NuPrep® skin prep gel (or other WAVi approved exfoliant) on the participant’s index finger (Figure 2.5.9).

Instruct the participant to rub and exfoliate both sides of their earlobes for 30 seconds to remove excess oils and dead skin. Make sure they remove all exfoliant gel from earlobes and fingers with a paper towel. Residual exfoliant gel on the earlobes may interfere with later steps.

Using the blunt needle syringe, fill the metal cup portion of the ear electrodes with electro-conductive cream (Figure 2.5.10). Make sure the cup is filled to the top. Underfilling the earclips may result in a poor quality EEG signal.

When using PPG earclips for HRV (Performance and Research only), do not apply electro-conductive cream directly to the earclips. Instead, apply a pea-sized drop via the blunt needle to the participant’s index finger and have them rub it onto their ear lobes. Excess electro-conductive cream on the PPG earclips could interfere with PPG measurement.

Clip the ear electrodes to the participant’s ears (Figure 2.5.11). Ensure the metal cups are making complete contact with the earlobe. The earclips are not right/left specific.

To achieve a tight fit, pull the headset down on the head. If needed, use the Boa Fit System® at the back of the headset. Pull the dial out until you hear a snapping sound. Pull both Boa® lines forward and attach the fastener hooks to the tabs with holes on the sides of the headset (Figure 2.5.12). Tighten the lines by pushing the Boa® Dial back in and turning clockwise.
Secure the ear electrodes to the magnetic posts on the headset (Figure 2.5.13). Ensure the magnets are sitting flat on the posts, as misalignment can lead to poor signal quality.

If using PPG earclips for HRV, connect the ear clip cables directly into the EPU via the two ports on the front of the EPU.

Taking care to keep the earclips properly positioned, place the headphones over the participant’s ears (Figure 2.5.14). The headphones help to further secure the headset in place. Allow the participant to adjust the headphones to achieve a comfortable fit as needed.

Insert the Electronic Processing Unit (EPU) securely into the port at the back of the headset (Figure 2.5.15). Connect the headphones to the EPU via the headphones auxiliary cable.

The EPU must be securely seated in the port at the back of the headset and connected to the laptop before proceeding.
F. Session Setup

After filling out the basic profile information, press the New Session button (Figure 2.6.1) located in the top right corner of the profile view.

Choose an appropriate session template from the popup window (Figure 2.6.2). Title the session using one of the suggested presets or type a custom title, then click OK.

Each session template includes a unique intake form, screening questionnaire(s), and recommended testing protocols for different situations. Every session includes at least the P300 Eyes Closed protocol. The user can add or subtract any intake form, screening questionnaire, or testing protocol from the session. Additionally, most reports may later be generated from any session type. (See the WAVi Reports section for more details)

Session Templates:

WAVi Behavioral: Appropriate for use when the test administrator suspects the presence of or has diagnosed disorders such as bipolar disorder, ADHD, anxiety or depression and wants to use standard public domain assessments (HAM-A, PHQ-9, ASRS-v1.1, and BSDS). Protocols included: P300 EC 4 Min, Flanker Test, Baseline EO 4 Min, Trail Making Test A, Trail Making Test B.

WAVi Behavioral Child: Appropriate for participants under the age of 18 when the test administrator suspects the presence of or has diagnosed pediatric disorders such as bipolar disorder, ADHD, anxiety or depression and wants to use standard public domain assessments (HAM-A, PHQ-9, DSM-5, and BSDS). Protocols included: P300 EC 4 Min, Flanker Test, Baseline EO 4 Min.

WAVi Concussion Study: Appropriate for use with athletes when the test administrator suspects the presence of a head injury. Includes both the Sport Concussion Assessment Tool 3rd and 5th Editions (SCAT3 and SCAT5), although only one of these should be filled out at any time. Protocols included: P300 EC 4 Min, Flanker Test, Trail Making Test A, Trail Making Test B, Baseline EO 4 Min.
**WAVi Performance:** Appropriate for use when the test administrator determines that a participant does not present with any neurological disorders. This template includes two HRV protocols (baseline and tracking), a general intake form, and no specific questionnaires.
Protocols included: Baseline EC 1 Min, P300 EC 4 Min, Tracking EO 1 Min.

**WAVi Scan:** This template is suitable for general EEG recording using a number of testing protocols automatically included. The WAVi Scan screening form includes all of the previously mentioned questionnaires for robust intake collection.
Protocols included: P300 EC 4 Min, Baseline EO 4 Min, Trail Making Test A, Trail Making Test B.

**WAVi Scan 20 Plus:** This template is appropriate for practitioners seeking to collect at least 20 minutes of EEG data. Some protocols are repeated more than once.
Protocols included: P300 EC 4 Min, Baseline EO 4 Min, Trail Making Test A, Trail Making Test B, P300 EC 4 Min, Flanker Test, Baseline EO 4 Min.

**WAVi Wellness Basic:** This template focuses on overall brain health and is the most basic template on the platform. This template includes the “basic“ wellness screening questionnaires (HAM-A, PHQ-9).
Protocols included: P300 EC 4 Min, Flanker Test, Trail Making Test A, Trail Making Test B.

**WAVi Wellness Plus:** Identical to the WAVi Wellness Basic template except for the inclusion of additional wellness screenings (MMSE, MoCA, HAM-A, GDS).
Protocols included: P300 EC 4 Min, Flanker Test, Trail Making Test A, Trail Making Test B.

After opening the new session, fill out the **intake form** as needed (see example in Figure 2.6.3). It is important to collect as much information in the intake form as possible.

While the participant is filling out the intake form, this may be a good time to make sure the headset is loaded with eSocs.

![Figure 2.6.3](image�)

**Session Time Remaining:** 1h 45m

![Figure 2.6.4](image�)

Every session has a time limit of 2 hours. After the 2 hour limit is reached, all forms and protocols in the session will become locked and cannot be modified. The remaining session time is located at the top left corner of the session screen (Figure 2.6.4).
G. Headset Contact and Signals

Verify that the bottom right corner of the main window shows the message “EPU Ready” (Figure 2.71). If not, check that the EPU is plugged into the laptop.

You are now ready to measure the eSoc contact and signal quality.

Visually inspect the headset and ensure the white tips of all eSocs are making contact with the scalp. If an eSoc is not making proper contact with the scalp, push it closer by gently pressing on the diamond band with your thumb.

Select the **Headset Contact** item from the queue on the left side of the session screen. This function measures the contact quality of each electrode location. It will first check the contact of the ground location and both ears. A green circle indicates good connection, yellow is acceptable, and red needs additional work (Figure 2.74).

It is important to strive for a green connection at the ground and both ear locations. However, yellow should suffice in a situation where a green signal is not attainable (Figure 2.74). If a better connection is needed, use the blunt needle syringe to add electroconductive cream to the ground location (Figure 2.73) in between the white tip of the eSoc and the scalp.

Once the ground and both ears show good or acceptable contact, press the **Check All Locations** button (Figure 2.75) located directly under the electrode diagram.
The software will automatically begin to measure the contact quality at each EEG electrode location, in groups of 2 or 3 locations at a time. Colored circles corresponding to each electrode location indicate good (green), acceptable (yellow) or unacceptable (red) contact quality (Figure 2.76).

After the software has finished automatically checking the headset contact, perform contact improvement techniques if needed, while simultaneously monitoring the screen for immediate feedback. Use the mouse or touch screen to select a particular electrode location where better connection is desired (Figure 2.77). Selecting a particular electrode location provides real time feedback of the contact quality at that location. Repeat contact improvement techniques until all locations show good or acceptable contact.

Basic contact improvement techniques include:

i. Moving Hair: Use your finger or blunt needle syringe to move hair until the eSoc is making direct contact with the scalp (Figure 2.78).

ii. Exfoliating the scalp: The eSocs are made of a material that can be used to exfoliate the scalp by rubbing back and forth or rotating to improve contact.

iii. Filling gaps: Use a blunt needle syringe with electro-conductive cream to fill gaps between the eSoc and the scalp (Figure 2.79).

iv. Adding additional liquid: Use a blunt needle syringe to add more saline solution to the eSoc.

For further troubleshooting help, please see the Troubleshooting Section.
After checking and improving the contact quality if needed, click the **Signal** tab at the top of the screen to inspect raw EEG waves (Figure 2.7.10).

Instruct the participant to close their eyes, relax their jaw, and remain still. Monitor raw waves for about one minute looking for acceptable signal quality.

![Figure 2.7.10](image)

If you observe drifting or noisy EEG traces (Figure 2.6.11), repeat contact improvement techniques until better signals are achieved (Figure 2.6.12).

It is important to remain calm and confident when striving for an improved connection.

Many raw EEG files will contain artifacts caused by movement, poor electrode-scalp contact, or other environmental factors. The **Instant Review** function allows you to identify artifacts in the EEG and proactively take corrective actions to improve data quality before running any protocols. To use this function, make sure the **Signal** tab is active (Figure 2.7.10) and allow the system to collect raw EEG waves for at least 30-60 seconds, indicated by a timer underneath the wave display. Instruct the participant to close their eyes and remain still. After sufficient data has been collected, press the **Instant Review** button (Figure 2.7.13). The segment of raw EEG data just acquired will be replayed automatically, with artifacts highlighted in red and blue. You can also manually scroll through the data by dragging the time slider or pressing the left/right arrow keys. To resume monitoring live EEG data, press the **Resume Live** button (Figure 2.7.14). Note: the Instant Review function does not become available until at least 15 seconds of data have been acquired.
**Black lines** indicate sections of acceptable EEG data.

**Blue lines** indicate possible EEG artifacts, which may also contain valid EEG data for P300 analysis. If these sections of EEG contain real artifacts, they will have a small impact on the accuracy of reported P300 values. These sections will be included for P300 metrics when generating reports.

**Red lines** indicate sections of data containing severe artifacts that will be excluded when generating reports.

If you observe numerous red lines (severe artifacts), take appropriate corrective actions, then press **Resume Live** and collect more data. Repeat this process until the data quality is improved.

Once you are satisfied with the contact and signal quality, inform the participant of the equipment's sensitivity to motion. Instruct them first to move, then blink their eyes, and finally clench their jaw to demonstrate how each of these actions affects the EEG (**Figures 2.7.15 & 2.7.17**). It is important for the participant to remain calm and relaxed during the test.

If some or all of the EEG traces have shifted up or down, or have disappeared off the screen, wait for those traces to return to their centerlines before starting any protocols.

If any of the EEG traces are wandering or noisy (as in **Figure 2.7.15**), add saline solution or electro-conductive cream to the specific electrode locations that are problematic. Adding additional liquid can sometimes help to achieve a cleaner signal. However, too much liquid can also cause electrical bridging between electrode locations. Take care not to oversaturate the eSocs, and wipe off any excess dripping liquid with a paper towel.
Open the **P300 EC 4 Min** protocol from the queue on the left side of the screen (Figure 3.1). The P300 is a 4 minute test.

Make sure the room is quiet and any bright lights are turned down. The mouse should be placed in the participant’s preferred hand. Ensure that the participant is sitting upright in a comfortable position and is resting their hand on the mouse. Check to see that the participant can keep both feet firmly planted on the floor or on a low stool. Dangling feet may cause movement artifact in the EEG during the test.

Inform the participant that two different audio tones will be presented once per second during the test: a low tone and a high tone. The participant must be able to clearly hear both tones in order to perform this test. If they cannot, check that the headphones are securely plugged into the EPU and are comfortably positioned over the participant’s ears.

Practice tones will be presented before the actual test is started. Instruct the participant to close their eyes, relax, and click the mouse whenever they hear the high tone. Either the left or right mouse button may be used. Clicks are indicated by green vertical lines on the raw wave display. It is important to confirm that mouse clicks are being registered by the software.

Synchronized eyeblinks (referred to as “Sync Blinks”) can occur if the participant blinks while clicking the mouse in response to rare tones. This results in a disproportionately high voltage seen in the frontal and surrounding locations. To reduce the likelihood of Sync Blinks or jaw clenching, have the participant tightly squeeze their eyes shut for a few seconds and then do the same with their jaw immediately prior to beginning the test.

**Note:** Try to limit the amount of instructional commands while explaining the P300 test, as over-explanation may stress the participant and decrease their cognitive resources.

Once the participant has practiced and completely understands how the P300 test works, press the green **Start** button to begin recording (Figure 3.1.2). The mouse cursor will be confined inside the raw wave display during the test. If you need to unlock the mouse before the test is finished, press the **Unlock Mouse** button using the touch screen or type ‘U’ on the keyboard.
The signal quality should still be monitored during testing. There may be some intermittent drifting signals due to motion, but raw EEG signals should appear clean for the majority of the test (See example of clean signals in Figure 3.14 below).

Realtime quality information is provided by the EEG Quality display (Figure 3.13). Red dots indicate excessive artifact in the signal at that location. Do not attempt to adjust the headset during a test, instead monitor the raw waves to determine the quality of the data. If there are numerous and persistent wandering waves, stop the test and restart after contact improvements have been made.

While the P300 test is in progress, vertical lines will appear over the raw wave forms (Figure 3.14). **Black vertical lines** mark the presentation of the common (low) tones. **Red vertical lines** mark the presentation of the rare (high) tones. **Green vertical lines** mark the clicks of the mouse. It is important to monitor the screen and confirm that the participant is clicking the mouse in response to the presentation of the high tones.

The WAVI P300 test is complete when the tones conclude and the raw waves automatically stop recording. If significant artifact was detected during the test, a yellow warning bar will appear at the bottom of the display in review mode. In severe cases, an additional warning message may also suggest that the test be re-run.

Now it is time to review the P300 test results.
4 Reviewing the P300 EC Protocol

There are several modes for reviewing P300 EEG data, each of which provides different information. Press the Display Mode button in the bottom left corner under the data display to see a menu of these modes (Figure 4.0.1).

A. Raw Wave + Quality Head

This mode displays the raw EEG waves recorded during the test, along with the signal quality of the currently displayed data segment. The data can be scrolled through using the time slider or the playback buttons on the right. This mode is especially useful for trained specialists when reviewing raw EEG signals (Figure 4.1).

B. P300

Use this mode to review P300 test waveforms and yield. The common and rare yields are indicated by the numbers to the right of each location (for example the number 39 in Figure 4.2.2). As 40 rare tones are presented, the red number should be close to 40 at a significant number of locations to ensure sufficient test yield (as seen in Figure 4.2.3).

The average P300 waveform response to the common tones is displayed in black (black wave in Figure 4.2.2). The average P300 waveform response to the rare tones is displayed in red (red wave in Figure 4.2.2). The dotted vertical line represents 300ms post rare tone presentation. The number of common and rare P300 responses included are displayed to the right of each location name in black and red, respectively (197 and 39 in Figure 4.2.2). Peak latencies and peak voltages are also displayed for each location beneath the location name and rare/common yield metrics.
C. Coherence

The Coherence display mode provides information related to the functional connectivity between cortical regions. This shows the coherence between pairs of EEG electrode locations in each frequency band, displayed in a topographic format (Figure 4.3.1). Coherence values range between 0.0 and 1.0. To reduce the complexity of the coherence displays, the coherence display threshold may be adjusted between 0.0 and 1.0. You can also touch any location on the screen to review the coherence between that location and all other locations. Coherence has been included for those more familiar with brain mapping and is considered an advanced topic for the purposes of this manual. See the WAVi Reports section for more information.

<table>
<thead>
<tr>
<th>Wavelength</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta</td>
<td>1.0 - 40 Hz</td>
</tr>
<tr>
<td>Theta</td>
<td>4.5 - 75 Hz</td>
</tr>
<tr>
<td>Alpha</td>
<td>8.0 - 13.0 Hz</td>
</tr>
<tr>
<td>Beta</td>
<td>13.5 - 20.0 Hz</td>
</tr>
</tbody>
</table>

Figure 4.3.2

D. Spectrum

The Spectrum display mode provides a magnitude spectrum (magnitude versus frequency) for each electrode location, displayed in a topographic format (Figure 4.4.1). The number displayed below the x-axis to the right of each location name indicates the frequency in Hz with the highest magnitude, typically in the alpha range. This display mode is included for those more familiar with brain mapping, and is considered an advanced topic for purposes of this manual. See the WAVi Reports section for more information.

Figure 4.4.1
Additional Protocols

A. Adding Protocols to Sessions

If you are not satisfied with the results of a protocol, or wish to take more data, you may add another protocol by pressing the Add to Queue button in the bottom left corner of the queue (Figure 5.1), selecting New Protocol, and then choosing an appropriate protocol template.

Unwanted protocols can be removed by pressing the Delete button, but care must be taken not to delete valid tests. If in doubt, do not delete.

Note: If you run back-to-back P300 Eyes Closed protocols, habituation may occur during the second test. This happens when subjects respond less strongly over time to the rare tone, causing the reported P300 voltages to decrease at one or more EEG electrode locations. It is best practice to give the participant a brief break before repeating the P300 protocol.

B. Flanker Test

The Flanker Test generates visual ERP metrics which complement those generated by the audio P300.

Select the Flanker Test protocol from the queue on the left side of the screen (Figure 5.2), or by adding it to the session as an additional protocol. An instructional screen will explain how to perform the test (Figure 5.2).

Figure 5.2.1

Figure 5.2

Figure 5.2.2
The Flanker Test is used for additional assessment of cognitive processing by testing the following functions: working memory, reaction time, automatic processing, and motor control. The number of correct responses will be reported at the end of the test.

- Instruct the participant to rest their hand on the mouse or on the left/right arrow keys located on the laptop's keyboard.
- A series of arrows will appear in the center of the screen at a rate of approximately one per second.
- Depending on the direction that the center arrow is pointing, the participant should respond with the corresponding mouse click or arrow key.
- The participant should respond as quickly as possible.
- If a mistake is made, reassure the participant by telling them that it is normal to make mistakes on this test and encourage them to continue.
- The results of the test will automatically appear upon completion of the test.
- Flanker waveforms will be displayed to the right of each EEG electrode location in a topographic format.
- Various Flanker reaction times will be displayed to the right of the Flanker waveforms.

See the W avi Reports section for more information on Flanker results.

C. Baseline EC 1 Min (Baseline HRV)
This protocol is included in a W avi Performance session and is a 1 minute eyes closed protocol. Instruct the participant to sit still and remain relaxed for the duration of the protocol.

Monitor raw EEG signals as well as the PPG signal. The PPG signal is shown in the bottom right corner of the display (see example in Figure 5.31).

![PPG-L](image)

Place focus in display window. Type L for left PPG, R for right PPG
H to toggle HRV display or M to display motion.

Figure 5.31

D. Tracking EO 1 Min (Tracking HRV)
This protocol is included in a W avi Performance session and is a 1 minute eyes open protocol. Instruct the participant to track the undulating waveforms with their breath by breathing in as the red wave rises and exhaling as the red wave falls (Figure 5.4).
NOTE: Only WAVi systems with PPG earclips can utilize HRV protocols. PPG earclips are not included with every WAVi system and are intended for research use only.

**E. Baseline EO 4 Min (Eyes Open Focused)**

This protocol is required to generate ADHD-related metrics which can be compared with the norms reported in the literature, such as the theta/beta ratio acquired at location Cz.

**F. Baseline EC 4 Min (Eyes Closed Resting)**

This protocol may be used in addition to the P300 EC 4 Min protocol if eyes closed data acquired during a non-stimulus condition is required. This is primarily useful where at least 20 minutes of EEG collection is required. Currently all of the Eyes Closed metrics displayed in the review mode, as well as in the reports, are computed from the background P300 EEG data rather than non-P300 eyes closed resting data.

**G. Trail Making Tests A/B**

Trail Making A & B tests engage cognitive resources involving visual processing, memory, motor function, spelling, and counting. The Trail Making tests can also provide information relating to visual search speed, scanning, speed of processing, mental flexibility, and executive functioning.

Select the **Trail Making Test A** protocol from the queue on the left side of the screen (Figure 5.71), or by adding it to the session as an additional protocol. A practice screen will appear (Figure 5.72).
Instruct the participant to use the touch screen to select the circled numbers in numerical order as quickly as possible. One or both hands may be used. The software may not register a selection unless the participant presses the pad of their finger directly on the correct number. When a correct selection is made, a gray line will be drawn to connect the circles, forming a trail. If a selection is not registered, this may indicate that the participant has not correctly selected the next number in the sequence. To fix their mistake, instruct the participant to press the last correctly selected circle and proceed with the test.

After the participant has practiced and completely understands the test, it is time to start. The test is comprised of the numbers 1-25, arranged randomly around the screen. When ready, instruct the participant to press the Start button (Figure 5.73) to begin the actual test.

Note: If a mistake is made, the participant must go back and press the last correctly selected circle before the software will allow them to continue.

Shown above is a completed Trail Making A test (Figure 5.74). The time displayed in the top left corner indicates how long it took for the participant to complete the test. Reference ranges will appear in the generated report.
Select the **Trail Making Test B** protocol from the queue on the left side of the screen, or by adding it to the session as an additional protocol. A practice screen similar to the one below will appear (Figure 5.8.1).

![Figure 5.8.1](image)

Instruct the participant to alternately select circled numbers and letters in numerical and alphabetical order (1-A, 2-B, 3-C, etc). The software may not register a selection unless the participant presses the pad of their finger directly on the correct number or letter. When a correct selection is made, a gray line will be drawn to connect the circles, forming a trail. If a selection is not registered, this may indicate that the participant has not correctly selected the next number or letter in the sequence. To fix their mistake, instruct the participant to press the last correctly selected circle and proceed with the test. **Note:** Inform the participant that it may be helpful to say the numbers and letters aloud.

![Start](image)

After the participant has practiced and completely understands the test, it is time to start. The test is comprised of numbers 1-13 and letters A-L. Make sure that the participant can distinguish the number '1' from the letter '1'. When ready, instruct the participant to press the **Start** button (Figure 5.8.2) to begin the test. **Note:** If a mistake is made, the participant must go back and press the last correctly selected number or letter before the software will allow them to continue.
Shown above is a completed Trail Making B test (Figure 5.8.3). The time displayed in the top left corner indicates how long it took for the participant to complete the test. Reference ranges will appear in the generated report.

**H. Trail Making Errors**

The last correctly selected number (Trail Making Test A) or number and letter combination (Trail Making Test B) will light up green after a short period of time if the participant has not made the next selection (Figure 5.8.1). If a mistake was made, the participant must go back and press the last correctly selected number or letter before the software will allow them to continue.
If the participant made any errors during testing, the final screen will display red lines where the errors occurred (Figure 5.9.2).
A. Generating a New Report

To generate a new report, press the **New Report** button (Figure 6.1) in the upper right corner of the profile screen.

![Screenshot of WAVi profile screen with New Report button highlighted.]

Select an appropriate report template from the dialog window (Figure 6.1.2), then press **OK**.

**Report Templates:**

- **Boone Report:** WAVi Test results with a Boone Brain Age score included.

- **Performance Report:** This report includes graphs of WAVi test results as well as muscle tension and HRV scores.

- **WAVi Behavioral Report:** WAVi test results with behavioral screening scores.

- **WAVi Child Behavioral Report:** WAVi test results with behavioral screening scores for children up to 17 years old.

- **WAVi Concussion Study Report:** WAVi test results with sports screening scores including SCAT3/5.

- **WAVi Scan Clinician Report:** This report is currently intended for use in research settings.

- **WAVi Scan Patient Report:** Similar to the performance report, except this includes Theta/Beta ratio instead of muscle tension, and omits HRV. This report is currently intended for use in research settings.

- **WAVi Wellness Basic Report:** WAVi test results with Wellness Screening scores.

- **WAVi Wellness Plus Report:** WAVi test results with Wellness Plus screening scores.
Select one to four sessions by checking the boxes to the left of the session titles (Figure 6.1.3). Selecting multiple sessions will allow for a comparison of data between those sessions. When ready, press OK in the yellow bar above the session list.

If any of the selected sessions contains multiple protocols of the same type, you will be asked to choose just one from that session. Typically this only occurs if extra protocols were manually added to the session.

Next, fill out the fields on the Basic Options tab (Figure 6.1.4). Depending on the report template, these may include fields for entering the practitioner’s name, suggested follow up times, and a box to specify customized recommendations for the participant or client.

If you wish to further customize the report, the Advanced Options tab (Figure 6.1.5) provides additional fields which allow you to adjust how certain metrics are calculated, add optional pages, and so on.

Both Basic Options and Advanced Options are customizable when generating any WAVi Report. Each report template provides slightly different options which can be selected and/or adjusted.

Note: Depending on the content of the selected sessions, the report template being used, and any selected options, some information may be missing or incomplete in the final report. In that case certain fields in the report may be left empty or labeled “N/A”. If this happens, you can either start over using a different report template, or adjust the options to better suit the available data.
When you have finished configuring the options, press the **Generate Report** button at the bottom of the window. It may take a few moments to generate the report. When the process finishes, the new report will automatically open in an external PDF viewer app.

After viewing the report, close it and return to the WAVi Desktop app. Press the **Finish** button at the bottom of the summary screen (Figure 6.16) to save the report to the participant’s profile.
B. WAVi Performance Report

Key Metrics

Brain Reaction Voltage  Brain Reaction Time  Physical Reaction Time

![Graphs showing metrics](image)

Figure 6.2.7

i. **Brain Reaction Voltage** - A measure of cognitive resources, in other words, a measure of the force with which the participant’s brain responded to the unique stimulus of the high-pitched tone. This metric is referred to as Audio P300 voltage in other reports and is derived from the EC P300 protocol.

ii. **Brain Reaction Time** - A measure of cognitive processing speed, in other words, a measure of how long it took until the participant’s brain responded to the unique stimulus of the high-pitched tone. This metric is referred to as Audio P300 delay in other reports and is derived from the EC P300 protocol.

iii. **Physical Reaction Time** - Physical reaction time to an audio stimulus is recorded when the participant clicks the mouse in response to the rare tone. This measure is different from the latency measure of brain speed. Physical reaction time is known to slow with trauma, aging, and other conditions.
Brain Reaction Voltage Map

Session 1  
(7/13/2019)  

Session 2  
(8/5/2019)  

Session 3  
(8/6/2019)  

Session 4  
(8/10/2019)  

---

iv. Brain Reaction Voltage Map - The topo(s) in the Brain Reaction Voltage Map are visual representations of the Brain Reaction Voltage measured at each of the 19 active EEG electrode locations during the EC P300 protocol.

Note: If any black dots are present in the topos (Figure 6.2.9), this is an indication of unacceptably low yield at the corresponding electrode locations.
**Muscle Tension**  
A measure of jaw and neck tension

---

**Frontal Alpha Balance**  
A measure of frontal symmetry

---

**What does your score mean?**  
This is a measure of muscle electrical activity at jaw and neck locations. Elevated levels may suggest muscle tightness.

---

**What does your score mean?**  
Tipping of the scale beyond the target range can be a decreased efficiency associated with stress, anxiety, or low moods.

---

Figure 6.2.10

---

**v. Muscle Tension** - A measure of electrical activity in the electrode locations closest to the neck and jaw.

---

**vi. Frontal Alpha Balance** - A measure of alpha symmetry in the frontal lobes. A score of 1.0 indicates symmetry between right and left.
Heart Rate Variability (System Balance)

Baseline HRV Score:
44/100
Previous: 15/100
Low scores may suggest short term stress.

Tracking HRV Score:
83/100
Previous: 83/100
Low scores may suggest long term stress.

HRV—

HRV or heart rate variability, is a measure of the variation between successive heartbeats. This measure provides insight into the function of the Autonomic Nervous system, or ANS, which is largely responsible for regulating such functions as heart rate, respiratory rate and digestion. Two critical branches of the ANS are the parasympathetic (“rest and digest”) and sympathetic (“fight or flight”) nervous systems. HRV provides a measure of the ANS as well as the balance between the parasympathetic and sympathetic systems.

vii. Baseline HRV Score— This score is derived from the Baseline EC 1 Min protocol. Generally, low scores can indicate short term stress.

viii. Tracking HRV Score— This score is derived from the Tracking EO 1 min protocol. Generally, low scores can indicate long term stress.
C. Other Report Types

The report below is the first page of the WAVi Wellness Basic Report, generated without Advanced Options (Figure 6.31).

**WAVi Wellness Basic Report**

<table>
<thead>
<tr>
<th>Session</th>
<th>Original Title</th>
<th>Change</th>
<th>Sleep</th>
<th>Since Meal</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Session 1 (7/30/2014)</td>
<td>Baseline</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>19 yrs</td>
</tr>
<tr>
<td>Session 2 (7/9/2015)</td>
<td>Baseline</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>20 yrs</td>
</tr>
<tr>
<td>Session 3 (2/11/2016)</td>
<td>End of Season</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>20 yrs</td>
</tr>
</tbody>
</table>

See Appendix for explanations of metrics shown on this page.

### Screening Scores

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton Anxiety Rating Scale (HAM-A)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>≤ 17</td>
</tr>
<tr>
<td>Patient Health Questionnaire-9 (PHQ-9)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

### Performance Assessments

<table>
<thead>
<tr>
<th>Test</th>
<th>Session 1 (7/30/2014)</th>
<th>Session 2 (7/9/2015)</th>
<th>Session 3 (2/11/2016)</th>
<th>Target Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Reaction Time (ms)</td>
<td>306 (±108)</td>
<td>256 (±73) 210 (±63)</td>
<td>269-387</td>
<td></td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>39-67 sec</td>
</tr>
<tr>
<td>Trail Making Test B</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>52-102 sec</td>
</tr>
</tbody>
</table>

### Evoked Potentials

<table>
<thead>
<tr>
<th>Test</th>
<th>Session 1 (7/30/2014)</th>
<th>Session 2 (7/9/2015)</th>
<th>Session 3 (2/11/2016)</th>
<th>Target Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Audio P300 Delay</td>
<td>300 ms</td>
<td>272 ms</td>
<td>260 ms</td>
<td>249-323 ms</td>
</tr>
<tr>
<td>Test/Retest Change</td>
<td>-</td>
<td>-28 ms</td>
<td>-40 ms</td>
<td>±11 ms</td>
</tr>
<tr>
<td>Audio P300 Voltage</td>
<td>15.2 µV</td>
<td>17.3 µV</td>
<td>19.4 µV</td>
<td>9-22 µV</td>
</tr>
<tr>
<td>Test/Retest Change</td>
<td>-</td>
<td>2 µV</td>
<td>4 µV</td>
<td>±2 µV</td>
</tr>
</tbody>
</table>

### State

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cz Theta/Beta</td>
<td>2.1</td>
<td>1.9</td>
<td>1.8</td>
<td>1.2-2.9</td>
</tr>
<tr>
<td>P3/F4 Theta/Beta</td>
<td>6.7</td>
<td>1.5</td>
<td>1.0</td>
<td>0.9-1.1</td>
</tr>
</tbody>
</table>

### Peak Frequency (7-13 Hz)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>8.8 Hz</td>
<td>8.5 Hz</td>
<td>9.0 Hz</td>
<td>8.6-10.5 Hz</td>
</tr>
<tr>
<td>Test/Retest Change</td>
<td>-</td>
<td>-0.2 Hz</td>
<td>0.2 Hz</td>
<td>±0.2 Hz</td>
</tr>
<tr>
<td>Central-Parietal</td>
<td>9.0 Hz</td>
<td>9.0 Hz</td>
<td>9.1 Hz</td>
<td>8.9-10.8 Hz</td>
</tr>
<tr>
<td>Test/Retest Change</td>
<td>-</td>
<td>0.0 Hz</td>
<td>0.1 Hz</td>
<td>±0.2 Hz</td>
</tr>
<tr>
<td>Occipital</td>
<td>9.0 Hz</td>
<td>9.0 Hz</td>
<td>9.2 Hz</td>
<td>8.9-10.8 Hz</td>
</tr>
<tr>
<td>Test/Retest Change</td>
<td>-</td>
<td>0.0 Hz</td>
<td>0.2 Hz</td>
<td>±0.2 Hz</td>
</tr>
</tbody>
</table>

**Maximum P300 Test Depth (µV) — Range: 240-500 ms — Topo scale referenced to Session 3**

BLACK DOTS INDICATE LOCATIONS WITH LESS THAN 20 CLEAN P300 RARE RESPONSES. TOPO COLORS AROUND DOTS MAY BE AFFECTED.

![Figure 6.31](image-url)
D. Screening Assessments

i. The Mini Mental State Examination (MMSE)

The MMSE is an instrument for screening cognitive function, commonly used to indicate the presence of cognitive impairment in a person with suspected dementia or following a head injury. Before administering the MMSE, it is important to make the participant comfortable (Figure 6.4.1).

Scoring:

<table>
<thead>
<tr>
<th>Score</th>
<th>Degree of Impairment</th>
<th>Formal Psychometric Assessment</th>
<th>Day-to-Day Functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-30</td>
<td>Questionably significant</td>
<td>If clinical signs of cognitive impairment are present, formal assessment of cognition may be valuable.</td>
<td>May have clinically significant but mild deficits. Likely to affect only most demanding activities of daily living.</td>
</tr>
<tr>
<td>20-25</td>
<td>Mild</td>
<td>Formal assessment may be helpful to better determine pattern and extent of deficits.</td>
<td>Significant effect. May require some supervision, support and assistance.</td>
</tr>
<tr>
<td>10-20</td>
<td>Moderate</td>
<td>Formal assessment may be helpful if there are specific clinical indications.</td>
<td>Clear impairment. May require 24-hour supervision.</td>
</tr>
<tr>
<td>0-10</td>
<td>Severe</td>
<td>Patient not likely to be testable.</td>
<td>Marked impairment. Likely to require 24-hr supervision and assistance with ADL.</td>
</tr>
</tbody>
</table>

Figure 6.4.1

ii. Geriatric Depression Scale (GDS)

This is a screening test for depression symptoms in the elderly. The GDS is used for evaluating the clinical severity of depression and monitoring treatment. It is easy to administer, needs no prior psychiatric knowledge, and has been well validated in many clinical environments. A score of 0-5 is normal while a score greater than 5 suggests depression.

iii. Adult ADHD Self-Report (ASRS-v1.1) Symptom Checklist

The Symptom Checklist is an instrument consisting of eighteen DSM-IV-TR criteria. Ask the participant to complete both Part A and Part B of the Symptom Checklist by selecting the box on the screen that most closely represents the frequency of occurrence of each of the symptoms. If a score of four or more is shown for Part A, then the participant has symptoms highly consistent with ADHD in adults and further investigation is warranted. It has been found that the six questions in Part A are the most predictive of the disorder and are often used as a screening instrument. The frequency scores on Part B provide additional cues and can serve as further probes into the participant's symptoms.
iv. The Patient Health Questionnaire (PHQ - 9)

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression. The PHQ-9 incorporates DSM-IV depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool.

To make a tentative depression diagnosis, the clinician should rule out physical causes of depression, normal bereavement and a history of a manic/hypomanic episodes. A depression diagnosis that warrants treatment, or a treatment change, requires that at least one of the first two questions be endorsed as positive (“more than half the days” or “nearly every day”) in the past two weeks. In addition, the tenth question, about difficulty at work or home or getting along with others, should be answered at least “somewhat difficult”. The following recommendations based on the PHQ-9 test must be made by a licensed health care practitioner (Figure 6.4.2).

<table>
<thead>
<tr>
<th>PHQ-9 Score</th>
<th>Provisional Diagnosis</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-9</td>
<td>Minimal Symptoms</td>
<td>Support, return in 1 month</td>
</tr>
<tr>
<td>10-14</td>
<td>Minor Depression Dysthymia, Major Depression, mild</td>
<td>Support, watchful waiting, Antidepressant or psychotherapy</td>
</tr>
<tr>
<td>15-19</td>
<td>Major Depression, moderately severe</td>
<td>Antidepressant or psychotherapy</td>
</tr>
<tr>
<td>&gt;20</td>
<td>Major Depression, severe</td>
<td>Antidepressant or psychotherapy</td>
</tr>
</tbody>
</table>

Figure 6.4.2

v. Hamilton Anxiety Rating Scale (HAM-A)

HAM-A is a common assessment of the severity of symptoms of anxiety in adults, adolescents, and children. Each item is scored on a scale of 0 (not present) to 4 (very severe), with a total score range of 0-56, where <17 indicates mild severity, 18-24 mild to moderate severity, and 25-30 indicates moderate to severe. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety).
E. Performance Assessments

i. Physical Reaction Time
Physical reaction time to an audio stimulus is recorded when the participant clicks the mouse in response to the rare tone. This measure is different from the P300 latency measure of brain speed. Physical reaction time is known to slow with trauma, aging, and other conditions.

ii. Trail Making
The Trail Making Test is a commonly used neuropsychological test that is sensitive to a variety of neurological impairments and processes. It provides information on visual search, scanning, speed of processing, mental flexibility, and executive functions. The time displayed at the end of the test is the amount of time taken to complete the task. The cognitive alternation required by Part B places demands upon executive functioning. Other cognitive resources, such as psychomotor speed and visual scanning, are also required to successfully complete the test. Studies show declining performance with increasing age, which form the basis of the age references presented on the reports (see Trail Making articles 1 and 2 in Appendix).

F. Evoked Potentials

i. Audio P300 Delay & Voltage
The WAVI P300 test generates event-related EEG responses which are time-locked to the audio presentation of rare high tones and common low tones. High tones are presented less often than the low tones on a random basis. Although the P300 is a positive voltage change occurring approximately 300 milliseconds after the rare tone is delivered (P3 in Figure 6.6.1), by convention it is displayed in an inverted form as a downward moving voltage. The amplitude (or depth) is considered to be proportional to the amount of attentional resources devoted to recognizing the rare tone, and the latency is proportional to a measure of cognitive classification speed.

The WAVI P300 protocol administers 200 common and 40 rare tones. The first page of the report indicates the largest amplitude in microvolts (μV) and shortest latency in milliseconds (ms) from the 6 central parietal channels alongside age-matched values into which 66% of participants are expected to fall. Typically, P300 latencies fall between 250-400 milliseconds.
An increase in latency and/or a decrease in amplitude has been observed in various conditions associated with reduced cognitive function including aging, dementia, depressive disorders, trauma, and vascular diseases. Some clinicians use this non-specific P300 measurement to investigate interventions that increase amplitude and/or decrease latency. Others use P300 as a basis for tracking participant progress. In the absence of a strong P300, longer latencies may be reported and it is suggested that in these cases the P300 waveforms be reviewed, along with literature associating long latencies with various conditions.

For comparison reports, the absolute test-retest changes from baseline are shown on the first page of the report in comparison to age-matched target ranges. (except the WAVi Performance Report and the WAVi Scan Patient Report)

G. State (Power)

i. Theta/Beta at Cz

The WAVi report compares the participant's theta/beta ratio to a target range. Theta/beta ratios are associated with cortical arousal and high theta/beta ratios have been shown to consistently differentiate between ADHD and normal samples with meta-analyses reporting up to 94% sensitivity and specificity.

Because the theta/beta ratio trait may be correlated with other conditions and with some medications, it has been suggested that this measure be used as a prognostic or screening indicator; rather than as a diagnostic tool, in conjunction with structured or semi-structured clinical interviews, well-standardized behavior rating scales of symptoms, and information collected from multiple sources.

See Theta/Beta at Cz articles 1-4 in Appendix for more information.

ii. F3/F4 Alpha Power

EEG studies have shown a link between hemispheric asymmetry in frontal regions of the cortex and depressive symptoms, with meta-analysis indicating moderately large effect sizes. This suggests that both depression and anxiety may be meaningfully related to relative frontal EEG asymmetry at rest. It has been proposed that an atypical pattern of resting frontal cortical asymmetry can serve as a stable, trait-like risk factor for the subsequent development of depression or other emotion related disturbances, where hemispheric specialization for cortical systems mediates motivational and emotional processes. See F3/F4 Alpha Power article 1 in Appendix for more information.

iii. Tension

Ask the participant to clench their jaw to demonstrate the effects of muscle tension on the EEG signals. The effects of muscle tension on EEG signals are typically in the beta frequency range. Since muscle tension in both the neck and jaw can be associated with a potential concussive impact and is associated with similar symptoms as a concussion, clinicians may want to manage this tension.
H. P300 Waveforms

P300 Waveforms are automatically included in all reports except the WAVi Performance Report and the WAVi Scan Patient Report.

P300s typically occur between 240 and 450 msec. Probable depth and latency of true P300 is indicated on 1st page of report. # Indicates yield. *Indicates possible artifact during late P300.

Figure 6.8.1
The Flanker metrics page (Figure 6.9.1) displays four average response times: Non Flanker, Congruent Flanker, Incongruent Flanker, and Combined.

- Non Flanker: Response time to single arrow presented facing right or left.
- Congruent Flanker: Response time to 5 arrows all aligned in the same direction.
- Incongruent Flanker: Response time to 5 arrows, four of which point in the opposite direction to the center arrow.
- Combined: The average combined time for all responses.

The Flanker test is used for assessing cognitive processing, particularly in the frontal and temporal lobes of the brain. The Flanker test engages cognitive functions including executive attention, working memory, reaction time, automatic processing, and motor control.
The Z-score option allows you to view color-coded graphs of absolute power, relative power, amplitude asymmetry, and coherence for all electrode locations (Figure 610.1). The colors represent Z-scores, taken from the WAVI wellness database as age-matched references, where dark blue and/or dark red represent participant values that are outside 3-sigma (top or bottom 0.15% of the normal reference) for that location. Z-score thresholds can be set in Advanced Options for the asymmetry and coherence plots to make graphs more readable. Z-scores have been included for those more familiar with EEG brain mapping and are considered to be an advanced topic for the purposes of this manual. Consult your WAVI Customer Support representative for further questions.
K. Eyes Closed P300 Spectrum

Alpha frequency range
8.0 Hz  13.0 Hz

FP1 8.5 Hz
FP2 8.5 Hz
F7  8.5 Hz
F3  8.5 Hz
FZ  8.5 Hz
F4  8.5 Hz
F8  8.5 Hz
T3  9.0 Hz
C3  9.0 Hz
CZ  9.0 Hz
C4  9.5 Hz
T4  9.0 Hz
T5  9.0 Hz
P3  9.0 Hz
PZ  9.0 Hz
P4  9.0 Hz
T6  9.0 Hz
O1  9.0 Hz
O2  9.0 Hz

Peak frequency analysis range: 7.0 - 13.0 Hz
* indicates questionable value.

Figure 6.11

The Eyes Closed P300 Spectrum option displays magnitude spectra (magnitude versus frequency) for each electrode location (Figure 6.11). The number below the x-axis represents the frequency with the highest magnitude in Hz (in the 7-13 Hz range), typically alpha. Alpha slowing has been seen in a number of conditions, including dementia or trauma. The Eyes Closed P300 Spectrum display is included for those more familiar with EEG brain mapping and is considered to be an advanced topic for the purposes of this manual. Consult your WAVi Customer Support representative for further questions.
L. Front - Back Connectivity (Coherence)

Coherence Network Graphs, P300 Eyes Closed
Row shows color-mapped coherence between head locations.

<table>
<thead>
<tr>
<th>Coherence Threshold: 0.4</th>
<th>Percent Change Threshold: 40</th>
<th>Comparison Mode: Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>THETA (4.5 - 7.5 Hz)</td>
<td>ALPHA (8.0 - 13.0 Hz)</td>
<td>BETA (13.5 - 20.0 Hz)</td>
</tr>
<tr>
<td>Session 1 (7/9/2015)</td>
<td>0.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Coherence is a measure of the correlation between two EEG locations as a function of frequency and provides information relating to the functional connectivity between cortical regions (Figure 6.12.1). Numerous studies (see Front Back Connectivity articles 1-3 in Appendix) have linked both absolute coherence values as well as changes in coherence to various conditions associated with reduced cognitive function, including trauma and mild cognitive impairment.
7 Troubleshooting

A. Headset Fit

There may be challenges fitting the headset on some participants. Applying the headphones can further secure the headset.

B. General Tips

Although obtaining consistently clean signals may be challenging, most issues with poor signal quality can be remedied with a little time and patience. Keeping both yourself and the participant relaxed and calm is essential to acquiring clean data.

After all locations have been checked using the headset contact screen, there are some tricks that help to achieve acceptable contact for locations still showing red or unacceptable connections. Using the touch screen or mouse, select the individual electrode location to receive immediate feedback on contact improvements.

- If the white tip of an eSoc is not touching the scalp, push it closer by placing your thumb over the diamond band and press gently to establish solid contact. Move hair from under the eSoc with your finger or the blunt needle syringe.
- If the gap is too large, replace standard eSoc with an extended eSoc. Make sure to soak the extended eSoc in 0.9% sodium chloride saline solution prior to placement. You can use an extended eSoc in any necessary location.
- If an eSoc is touching the scalp but is not showing good contact, this may be due to excess dead skin in the area. The eSocs are made using a material that can be used to exfoliate the scalp by rubbing back and forth or rotating to improve contact.
- Add extra saline solution to the eSoc or electro-conductive cream between the eSoc and the scalp. Sometimes applying extra conductive cream is all it takes to achieve better contact.

Important: Do not rely solely upon observing a green contact at a particular electrode location. It is equally important to monitor raw waves prior to the P300 protocol to verify sufficient signal quality.
C. Raw Wave Monitoring

- To improve drifting raw wave signals, use general troubleshooting techniques. The term drifting is used herein to describe EEG waveforms which move significantly above and/or below the horizontal display screen areas to the right of the name of the EEG electrode locations indicating where they were recorded.
- If no raw EEG signals can be observed, try restarting the WAVI Desktop software and unplugging the EPU cable from the laptop. Reconnect the EPU and allow it to initialize prior to reentering the software. Sometimes a computer restart is necessary.
- If any troubleshooting involves a software exit and restart, it is best to find and reopen the same session to retain all intake information. This prevents the participant’s profile from becoming cluttered with incomplete sessions, and makes report generation less confusing. (Note: the session must be reopened before the 2 hour lock limit is reached.)
- The most important tip is to have patience. Obtaining a clean signal may take more time for some people. Just remember that it is possible to obtain data for everyone, but sometimes more effort is required.

D. Connection Issues (intermittent or loose connections)

- If noisy signals are still present after completing contact improvement techniques, apply Paul Mitchell© The Cream (or other WAVI approved solution) to the ground eSoc. Ensure the ear electrodes are laying flat on the ear posts and that the ear clips are firmly connected to the earlobes.
- There will be either random noise or no signal if the EPU is not completely attached to the headset. Without removing the EPU from the headset, confirm that it is securely attached.
- Sometimes even though a green contact circle is displayed for a particular electrode location, the corresponding EEG signals may still be drifting. This may be due to the eSoc making contact with only the hair and not the scalp, causing a poor connection that needs to be modified. In this case, move hair from under eSoc and add electro-conductive cream to the location.

E. Dead Channels

On rare occasions an EEG channel location in the WAVI headset may fail. This may appear in the raw EEG display as a flat line for that channel. As long as the failed channel is not the ground, you can still collect data and complete the session. Immediately following the session, contact WAVI customer support for return and replacement instructions.

F. Significant Amounts of Signal Noise

In some rare cases, signal noise may persist even if good contact is being shown by the contact check function. If you experience this, check the EPU by making sure it is properly plugged and seated into the headset and also connected to the computer via the USB cable.
- Check the ground and ear electrodes.
- Check the room for nearby electrical devices that may interfere with signals, such as mobile phones.
- Excess muscle tension or participant movement may play a role in generating extra noise. Make sure that the participant is both calm and relaxed.
To solve the problem it may be necessary to replace the headset.

- If the problem occurs with a different headset as well, but only intermittently, check for external electrical noise. If this problem occurs on another participant with the same headset, call WAVi immediately for a replacement.
- Call WAVi customer support if the problem continues and does not improve with WAVi troubleshooting techniques.

G. Hairstyle Challenges

There are many different hairstyles that can present challenges when trying to achieve a clean signal. However, successful scans have been performed on nearly every hairstyle.

Testing someone with thick hair may require more time to obtain acceptable contact. It is important to remain calm and keep the participant at ease throughout the entire process.

For participants with thick hair, it is sometimes difficult to get the normal eSocs to make direct contact with the scalp, so extended eSocs should be used. The headphones can also be used to help secure the headset down.

Ensure that eSocs are making contact with the participant’s scalp and not hair or braids. Sometimes a poor contact is shown because there is too much hair between the eSoc and the scalp. Use the blunt needle syringe or your finger to push hair out from under each eSoc.

In some cases, there may be too much hair to solve any problems by using the headphones or moving the hair to the side. If necessary, it is possible to pull pieces of hair through the holes of the headset to reduce the amount of hair underneath.
8 Care and Maintenance

After all testing is complete, remove all eSoc electrodes from the headset by pushing on the back of the diamond bands until the eSocs pop out. After removal from the headset, discard all used eSocs. WAVi eSocs are meant for one-time use and must be discarded after every session for sanitary reasons.

- Dispose of the blunt needles.
- Thoroughly dry the headset with a paper towel to remove saline.
- Remove gel from the ear electrodes with alcohol prep pads.
- Wipe down the entire WAVi Headset with alcohol prep pads.

A. Lifetime Care

While the WAVi Headset has been designed for ease of use, it should always be handled with care. Please note the following:

- Use only alcohol prep pads to clean the components of this device. Do not use cleaning agents or solvents on any system components.
- Never immerse the WAVi Headset in liquids of any kind.
- Never expose the WAVi Headset to extreme temperatures.
- Exercise care as rough handling may adversely affect the device’s operation.
- As with any electronic device, protect the WAVi Headset from impact, exposure to moisture, liquid spills, sand, dirt or debris.
- Periodically inspect for any signs of damage.

B. Operation, Storage and Transport

The WAVi Headset should be operated within:

1. Ambient temperature range: 50°F (10°C) to 104°F (40°C).
2. Relative humidity range: 30% to 75%.

If the device is stored or transported in temperatures outside this range, allow the device time to return to room temperature before use.

Transport the WAVi Headset in the WAVi portable bag.

Handle with care.
Appendix F

WAVi™ U.S. Food and Drug Administration Clearance

April 28, 2017

WAVi, Co.
David Jones
FDA Consultant
3535 S Irving St.
Englewood, Colorado 80110

Re: K162460
Trade/Device Name: WAVi™ Headset and WAVi™ eSoc™ Single Use Electrode Contacts
Regulation Number: 21 CFR 882.1320
Regulation Name: Cutaneous Electrode
Regulatory Class: Class II
Product Code: GXY
Dated: March 22, 2017
Received: March 31, 2017

Dear Mr. Jones:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA’s issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in
the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely,

Michael J. Hoffmann -S

for Carlos L. Peña, PhD, MS
Director
Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure
Indications for Use

The WAVi Headset is intended for use in routine clinical and research settings where rapid placement of a number of EEG electrodes is desired.

Type of Use (Select one or both, as applicable)

☐ Prescription Use (Part 21 CFR 801 Subpart D)  ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

This section applies only to requirements of the Paperwork Reduction Act of 1995.

"DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW."

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fas.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."
510(k) SUMMARY

Submitted by: WAVi Co.
3535 S. Irving Street
Englewood, CO 80110
804-909-2389

Contact Person: David Jones
281-989-8515

Date Prepared: April 28, 2017

Proprietary Name: WAVi™ Headset and WAVi™ eSoc™ Single Use Electrode Contacts

Model Numbers: WH-100: XS Headset
WH-200: S Headset
WH-300: M Headset
WH-400: L Headset
WH-500: XL Headset

Common Name: EEG 10-20 Electrode Headset and Electrodes

Classification: Class II: 21 CFR § 882.1320

Classification Name: Cutaneous Electrode – GXY

Predicate Devices: Electro-Cap™ System (K112319)
Electro-Cap™ Intl., Inc.
1011 West Lexington Rd.
Eaton, OH 45320

Device Description:
The WAVi™ Headset is an EEG electrode positioning system used to quickly place the electrodes in a uniform and consistent manner in accordance with the international standard Ten-Twenty System (10-20) to acquire electrophysiological EEG signals from an individual to a suitable EEG data collection device.

The device consists of the WAVi™ Headset, WAVi™ eSoc™ Single Use and Tin Electrode Contacts; the head set comes in five models/sizes (XS, S, M, L, XL). This device is portable, non-sterile, non-invasive, non-radiation emitting, point-of-care use device for use in healthcare facilities and hospitals.

Device characteristics include the eSoc™ Single Use Electrode Contacts which are soaked in 0.9% Normal Saline which is unique as it serves as the electro-conductive material and patient contact allowing the brain’s electrical signals to be read through an EEG data collection device. Typical set-up and procedure time is less than twenty minutes.

The device does not contain software, biologics, drugs, coatings or any claim of sterility.
The WAVi™ Headset, eSoc™ Single Use and Ear Electrode Contacts are made from well-established medical grade materials; the Headset is made from a proprietary EVA material with tin plated ring electrode ports for placement of the Nylon 101 WAVi™ eSoc™ Single Use Electrode Contacts, and two ear electrodes are also made from Tin. A wire harness is embedded between two layers of EVA and is attached to each electrode port. The wire harness exits the headset to a 32-pin connector port.

**Intended Use:**

The WAVi Headset is intended for use in routine clinical and research settings where rapid placement of a number of EEG electrodes is desired.

**Technological Characteristics**

The following is a side-by-side of the WAVi device compared to the Predicate:

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>WAVi Co.</th>
<th>Electro-Cap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name</td>
<td>WAVi Headset</td>
<td>Electro-Cap System (K780045)</td>
</tr>
<tr>
<td><strong>Indication for Use</strong></td>
<td>The WAVi Headset is intended for use in routine clinical settings where rapid placement of a number of EEG electrodes is desired.</td>
<td>The Electro-Cap is intended for use in routine clinical settings where rapid placement of a number of EEG electrodes is desired.</td>
</tr>
<tr>
<td><strong>Environmental Use</strong></td>
<td>Electrophysiological</td>
<td>Electrophysiological</td>
</tr>
<tr>
<td><strong>Target Patient</strong></td>
<td>Adults and Children</td>
<td>Adults and Children</td>
</tr>
<tr>
<td><strong>Where Used</strong></td>
<td>On the head</td>
<td>On the head</td>
</tr>
<tr>
<td><strong>Anatomical Contact Sites</strong></td>
<td>Patient’s skin (scalp)</td>
<td>Patient’s skin (scalp)</td>
</tr>
<tr>
<td><strong>Number of Contacts</strong></td>
<td>22</td>
<td>2 to 256</td>
</tr>
<tr>
<td><strong>Sterile</strong></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Size of Cap</strong></td>
<td>Various- Extra Small to Extra Large</td>
<td>Various- Extra Small to Large</td>
</tr>
<tr>
<td><strong>Style of Cap</strong></td>
<td>Full Head Cap</td>
<td>Full Head Cap</td>
</tr>
<tr>
<td><strong>Cap Material</strong></td>
<td>EVA</td>
<td>Spandex</td>
</tr>
<tr>
<td><strong>Location of Wiring</strong></td>
<td>Inside Cap</td>
<td>Inside Cap</td>
</tr>
<tr>
<td><strong>Type of Cables</strong></td>
<td>Standard Ribbon Cable and Lead Wires</td>
<td>Standard Ribbon Cable and Lead Wires</td>
</tr>
<tr>
<td><strong>Type of Electrode Drop</strong></td>
<td>Detachable and Non Detachable</td>
<td>Detachable and Non Detachable</td>
</tr>
<tr>
<td><strong>Electrode Material</strong></td>
<td>Nylon 6/6 (101) and Pure Tin</td>
<td>Pure Tin</td>
</tr>
<tr>
<td><strong>Electrode Placement System</strong></td>
<td>The International 10-20 System is used as a basis for the electrode placement.</td>
<td>The International 10-20 System is used as a basis for the electrode placement.</td>
</tr>
<tr>
<td><strong>Number of Recording Channels</strong></td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td><strong>Electrode Positions Utilized</strong></td>
<td>Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C3, T4, T5, P3, Pz, P4, T6, O1, O2, A1, A2</td>
<td>Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C3, T4, T5, P3, Pz, P4, T6, O1, O2, A1, A2</td>
</tr>
<tr>
<td><strong>Type of Connectors</strong></td>
<td>D-Sub Connectors, Touch Proof Din Sockets and Special Connectors to Match EEG Equipment and Computers</td>
<td>D-Sub Connectors, Touch Proof Din Sockets and Special Connectors to Match EEG Equipment and Computers</td>
</tr>
<tr>
<td><strong>Biocompatibility Testing</strong></td>
<td>None was conducted</td>
<td>None was conducted</td>
</tr>
</tbody>
</table>
The electrical activity of the brain is acquired through 0.9% Normal Saline soaked eSoc™ inserted into the electrode ports and connected through the Headset’s wiring harness to the Patient Cable which is connected to the EEG device where brain activity may be recorded for evaluation.

Non-Clinical Testing:
The WAVi™ Headset and accessories are manufactured of medical grade materials including ethylene vinyl acetate (EVA), nylon 6/6 (101) and tin. Multiple 510 (k)'s have been cleared for each of these materials demonstrating no need for further biocompatibility testing.

The WAVi™ Headset and accessories’ Quality Assurance testing includes visual inspection of the headset, label and labeling, dimensional verification, and individual electrode resistance of the components and finished product. The WAVi™ Headset and accessories meet all performance specifications.

The WAVi™ Headset and the Electro-Cap™ System were compared for sizing, electrode placement and labeling, and was found to be substantially equivalent.

The WAVi™ Headset and the Electro-Cap™ were also compared side-by-side on three test subjects using a Lecoir Neurosearch-24 Brain mapper (K915820); the spectral shape and maximum frequency of the corresponding WAVi™ Headset and Electro-Cap spectrums at each of the 10/20 EEG locations were consistently similar within each subject.

Substantial Equivalence
The WAVi™ Headset, WAVi™ eSoc™ Single Use and Tin Ear Electrode Contacts are portable, non-sterile, non-invasive, non-radiation emitting, point of care, electroencephalogram (EEG) devices, and is intended for use in routine clinical and research settings where rapid placement of a number of EEG electrodes is desired.

All non-clinical tests demonstrate that the WAVi™ Headset and accessories are as safe, as effective, and perform as well as or better than the legally marketed predicate device.

The WAVi™ Headset is substantially equivalent to the predicate devices in the following manner:

- Same intended use
- Same operating principle
- Same fundamental scientific technology
- Same or substantially equivalent materials, including headset and electrodes.

There are no other substantial or significant differences between the WAVi™ Headset and its’ accessories and the predicate that would affect safety, effectiveness or performance, therefore the WAVi™ Headset and accessories’ are substantially equivalent to the predicate device.