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Association between brain oscillations and alertness in early post-operative recovery

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Thesis

ASSOCIATION BETWEEN BRAIN OSCILLATIONS AND ALERTNESS IN EARLY POST-OPERATIVE RECOVERY

by

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“Anesthesia is quite remarkable. It’s lost time.” -Michael Keaton

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ABSTRACT

The aging population and increase of ambulatory surgeries have greatly increased strain on surgical and post-surgical staff that decreases the safety of care. Our overall goal is to find ways to decrease the time of anesthetic recovery to allow for more efficient post-surgical treatment. The specific aims of this study were to assess the correlations between neurocognitive recovery measures of attention and vigilance to brain dynamics. We analyzed reaction time via auditory psychomotor vigilance testing (aPVT) testing and the Richmond agitation-sedation scale (RASS) scores in 145 patients prior to and preceding surgery. Intraoperative electroencephalogram was also recorded for 115 of those patients. Data was analyzed to associate aPVT performance to recovery time and intraoperative brain dynamics. We found an association coefficient between reaction time and RASS recovery of 0.022 (p-value = 0.0001) showing a significant association. Further, we found age to be a significant confounding variable (p=0.04421) and included this in our association model. Lastly, there was no significant association found between intraoperative burst suppression and reaction time values (p=0.497). Overall, aPVT was found to be a robust test to assess recovery timeline in peri-operative anesthesia care unit patients. These results highlighted the potential use of an objective metric to track neurocognitive recovery after anesthesia, especially in elderly patients undergoing surgery.

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LIST OF ABBREVIATIONS

aPVT .... Auditory Psychomotor Vigilance Testing

ASA... American Society of Anesthesiologists

BSO... Burst Suppression Occurrence

EEG.. Electroencephalography

GABA .... Gamma-Aminobutyric Acid

$GABA_AR$ .... Gamma-Aminobutyric Acid type A Receptors

ICU.. Intensive Care Unit

MAC .... Minimum Alveolar Concentration

NMDA .... N-Methyl-D-Aspartate

PACU .... Post-Anesthesia Care Unit

RASS.. Richmond Agitation-Sedation Scale

RT .... Reaction Time

INTRODUCTION

Neurocognitive Recovery from Anesthesia

Over 50 million patients undergo major surgical procedures every year in the United States. The cost of patient recovery has not only financial implications, but also safety implications. Before 2019, medical staff had already been overburdened due to understaffing. A study conducted just prior to the pandemic showed that for every additional patient a nurse had on a floor, the odds that the nurses or patient would give a lower safety rating increased.[1] The introduction of the COVID-19 pandemic has since greatly exacerbated this issue. Studies conducted during the pandemic found that understaffing was significantly related to nurses having to perform safety workarounds in order to complete their work for all patients.[2] Most hospitals across the country current day are considered understaffed with beds constantly at capacity, increasing the workload and safety concerns from overpopulated hospital floors.[3] Thus, minimizing the beds utilized for post-operative recovery will reduce the patient load for hospital personnel to allow for more thorough and safer patient care. Research can help reduce this burden by creating predictive models and thus a clear guideline of post-anesthetic recovery for individual patients. The future of personalized anesthetic care is based in ensuring neurocognitive recovery occurs at an efficient speed by individualizing medications based on tested biomarkers, to decrease recovery time and thus patient volume in hospitals.

Surgical anesthesia is one of the most dramatic chemical manipulations of the brain. Many studies have been conducted in an attempt depict the chemical interactions at an electrical magnitude. Through these studies, it has been found that sleep inducing anesthesia exposure during surgeries lead to long-term and short-term neurocognitive impairments. Some of these long-term impairments are severe: coma, death, and nerve sensitivity loss. More commonly, short-term impairments, for example, post-operative delirium (POD), highlighting attention deficits, and post-operative cognitive dysfunctions (POCD), focused on memory and other higher functions, cause longer hospital stays and increases medication requirements during recovery. Patients most at risk for these complications are typically older patients.[4,5]

Brain Health

A main feature of a ‘healthy’ brain is the plasticity, i.e., the ability to recover after changes, such as anesthesia and surgery. Brain aging results in physiological changes, with or without presence of neurodegenerative diseases, such as loss of myelin, white matter, and cortical size, and an increase in beta-amyloid plaques, among other altered proteins.[6] All of these cortical changes have been found to, over time, affect brain plasticity and functioning. Thus, finding cognitive markers throughout the surgical recovery period that suggest either a faster or slower post-surgical recovery may open up possibilities to use these markers as indicators of brain health. Furthermore, there is evidence that anesthesia/surgery exposure leads to long-term neurocognitive impairment after the procedure. Finding biomarkers that correspond with longer post-operative recovery may provide more information on the brain structures that anesthesia has lasting effects. Alongside this, it may illustrate which systems are most vulnerable to the first stages of neurocognitive impairment and degeneration.

In the 20th century, we are approaching a new issue in healthcare. The world population is aging faster than in previous years, as birth rates and death rates are concurrently decreasing. From 2009 to 2019, the population over the age of 65 in The United States increased by 36% and is expected to see another increase of 21.6% in the next 20 years.[7] This leads to a multifaceted burden on the system, as more patients each year require surgery with less workers to care for these patients. Within all of these implications in mind, mapping the healthy brain as well as markers of decline should be at the forefront of current research to prepare for the increasing elderly populations. Finding patterns within the recovery process is a part of this puzzle that can help relieve the burdens associated with these costs on the healthcare system.

Intraoperative Anesthetics

To explore how to better analyze post-operative recovery, the physiological changes that occur during surgery must first be understood. General anesthesia is defined as anesthetic usage that fulfills four requirements: unconsciousness (anesthesia), analgesia (lack of pain sensation), amnesia (lack of memory), and lack of movement in response to painful stimuli. Surgical anesthesia typically utilizes a combination of gases and intravenous drugs; the most commonly used of these drugs being GABAergic drugs.

Mechanisms and Effects of GABAergic Anesthetics

Gamma aminobutyric acid (GABA) is an inhibitory neurotransmitter and works as the main effector in the brain and spinal cord- the main targets of surgical anesthesia. GABAergic anesthetics are widely used to induce rapid loss of consciousness and amnesia.[8] Propofol, a widely used intravenous drug, amplifies the inhibitory effects of

GABA on postsynaptic surface receptors subunits (illustrated in Figure 1 below) of the CNS. Propofol is as a highly attractive anesthetic drug due to its ability to produce rapid onset of desired effects with a short half-life.[9] The inhibitory effects are amplified via prolonged opening of chloride channels, which produces a hyperpolarized state in the cell membrane. This prevents rapid depolarization and thus slows action potentials, i.e., neuronal communication in the thalamocortical system. Propofol is able to induce a characteristically recognizable effect through promotion of slower cortical waveforms known as delta oscillations, which will be further considered in this discussion.[10] The slowing of these waveforms and neuronal connection produces the loss of consciousness that is desired in surgical operations. Propofol is often given in a large bolus at the beginning of induction, and intravenously supplied throughout the procedure at varying dosages, dependent on the surgery's demands.

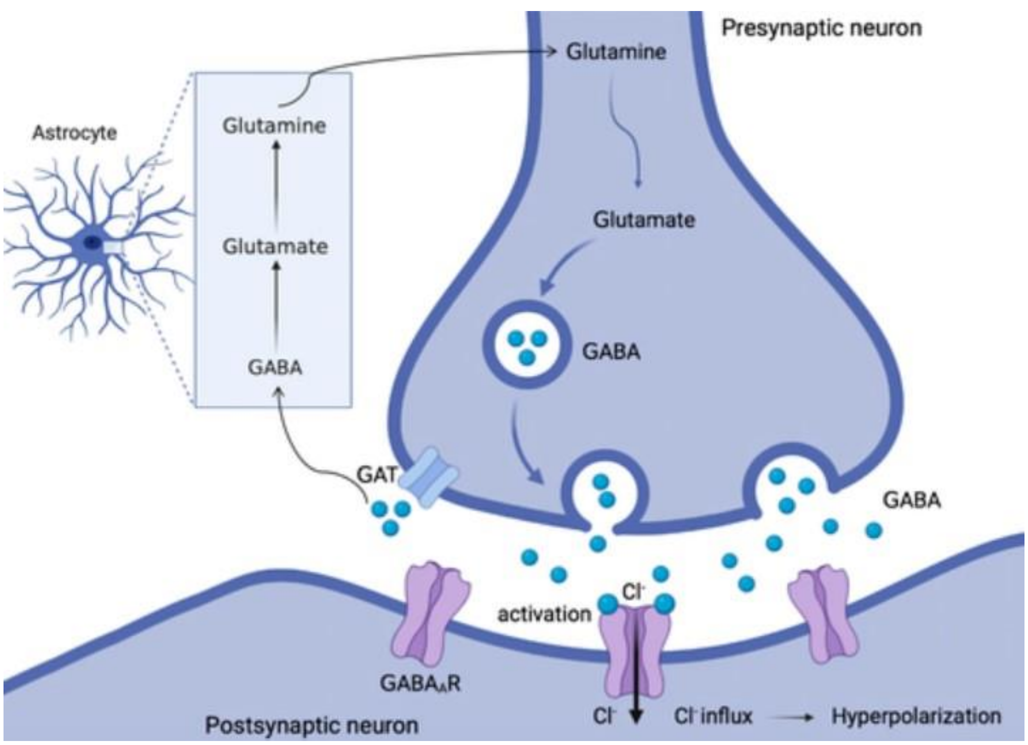


Figure 1. GABA inhibitory effects. GABA opens chloride channels, allowing an influx of Cl- into the postsynaptic neuron, hyperpolarizing the postsynaptic membrane. Propofol prolongs GABA inhibitory effects on the $GABA_AR$ ion channels. Adapted from Lou and Balle, 2022.[11]

It is important to note that while GABA-A neurotransmitters are one of the main receptors effected by anesthetic medications, they are not involved in one of the main constructions of anesthesia- analgesia or suppression of pain receptors. Other receptors such as nicotinic acetylcholine (Ach) and N-methyl-D-aspartate (NMDA) neurotransmitters provide analgesic effects intraoperatively. NMDA neurotransmitter receptors allow the perception of pain through glutamate's excitatory effects on the cell by opening positively charged ion channels, for ions such as calcium, and thus depolarizing postsynaptic membranes. Some of the main operating room NMDA antagonists used to prevent the upregulation of ion channels include ketamine and dexmedetomidine; however, these medications are not used on all patients and other medications may be supplemented to achieve analgesia.[12]

Mechanisms and Effects of Inhaled Anesthetics

Isoflurane and sevoflurane are two other major anesthetics used during general anesthesia. Unlike propofols intravenous delivery, isoflurane and sevoflurane and inhaled ether anesthetics effect a multitude of receptors in the body, including GABA sensitive receptors. These anesthetics are mildly soluble in blood and thus have quick transport throughout the circulatory system, allowing for a rapid onset of desired effects, like propofol.[13] However, the half-life of these medications is much larger than propofol, and thus take longer for effects to wear off after dosage has concluded. Inhaled anesthetic potency is measured in terms of minimal alveolar concentration (MAC) values, which "is defined as the concentration of inhaled anesthetic within the alveoli at which 50% of people do not move in response to a surgical stimulus", which thus achieves the fourth goal of anesthesia: lack of movement to painful stimuli.[14] However, the values present are calculated by measuring the inhaled anesthetics compared to the end-tidal volume of anesthetics, finding the difference as a value that in the operating room tends to range from 0.2 (considered MAC-awake) up to 1.5 in cases that require heavy inhaled anesthetics that are low in potency/solubility. The importance of oscillations produced by these inhaled anesthetics will be discussed later.

Effects of Anesthetics on Cognition

The long-term mechanistic effects of exposure to anesthetics have been heavily researched in animal models. Within these studies, they have found lasting effects of overexpression of GABA subunits on neurons and desensitization to GABA neurotransmitter that have led to subtle long-term degradation in cognitive function.[15,16] Other animal studies focused on specific anesthetics, such as sevoflurane, and showed correlations between sevoflurane exposure and apperance of tau phosphorylation- one of the main brain health physiology factors that is indictive of increased risk for Alzheimer's disease.[17] While these effects have not been measured in human patients due to the invasive nature of data collection, there have been human studies that clearly correlate a diminished cognitive state after exposure to anesthetics, especially in the elderly.[18,19,20] These results, when compared to animal studies, raise important questions on long-term effects of anesthesia on cognitive impairment. These effects need to be studied further in human models to fully understand the negative effects of general anesthetics and how to personalize medications to minimize these negative effects.

Electroencephalography

While loss of consciousness and response to pain are typical easy to evaluate while a patient is under surgical sedation, it is difficult in the last two purposes of anesthesia: analgesia and amnesia. This is where electroencephalography becomes an important tool for anesthesiologists. The usage of electroencephalography (EEG) has been vastly growing since its adoption into clinical medicine in 1950's, from diagnostic purposes to real time evaluations of conciousness.

Electroencephalography is an instrument used to measure the electrical activity of the brain via electrodes placed on the scalp. Electrodes can be invasive, using subdermal needle electrodes, or non-invasive using sticker electrode. In either case, brain activity is measured by passive recording of the pyramidal neurons of the cerebral cortex. The electrical activity is presented in real time in either waveforms or a power spectrum. Through monitoring brain oscillations, depth of anesthetics can be evaluated.

Oscillations in an electroencephalogram (EEG) are classified into five different waves, with the increasing frequencies as follows: Delta waves (up to 4 Hz), theta waves (4-7.5 Hz), alpha waves (7.5-12 Hz), beta waves (12-30 Hz), and gamma waves (above 30 Hz). The wave frequencies are representative of neuronal pathway communications. Waveform biomarkers have been identified on EEG spectrograms for individual anesthetics, such as alpha and slow-delta oscillations induced by propofol, producing high power readings on the spectrogram.[10] Both isoflurane and sevoflurane have been found to influence the oscillations similar to propofol, showing slow-delta oscillations (1-4 Hz), as well as alpha oscillations (8-12 Hz).[10] However, as these inhaled anesthetics approach MAC level, the oscillations show distinct theta oscillations. Thus, anesthesiologists are able to visualize both the onset of the anesthetics through the described patterns, as well as the dissipation of this anesthetic as the oscillations return back to baseline lower amplitudes and higher frequencies, towards beta oscillations and lower frequencies on the spectrogram.

Intraoperative EEG is also important in identifying burst suppression- a pattern on the compressed spectral array in which a span of isoelectricity (no waveforms) occurs, with intermittence of high frequency oscillations known as ‘bursts,’ before returning yet again to isoelectricity, as illustrated below in Figure 2. This figure also illustrates the alpha waves previously discussed with both propofol and sub-MAC anesthetic concentrations. Underneath the illustration of burst suppression, we are able to see an example of pure isoelectricity, or full brain electricity suppression.

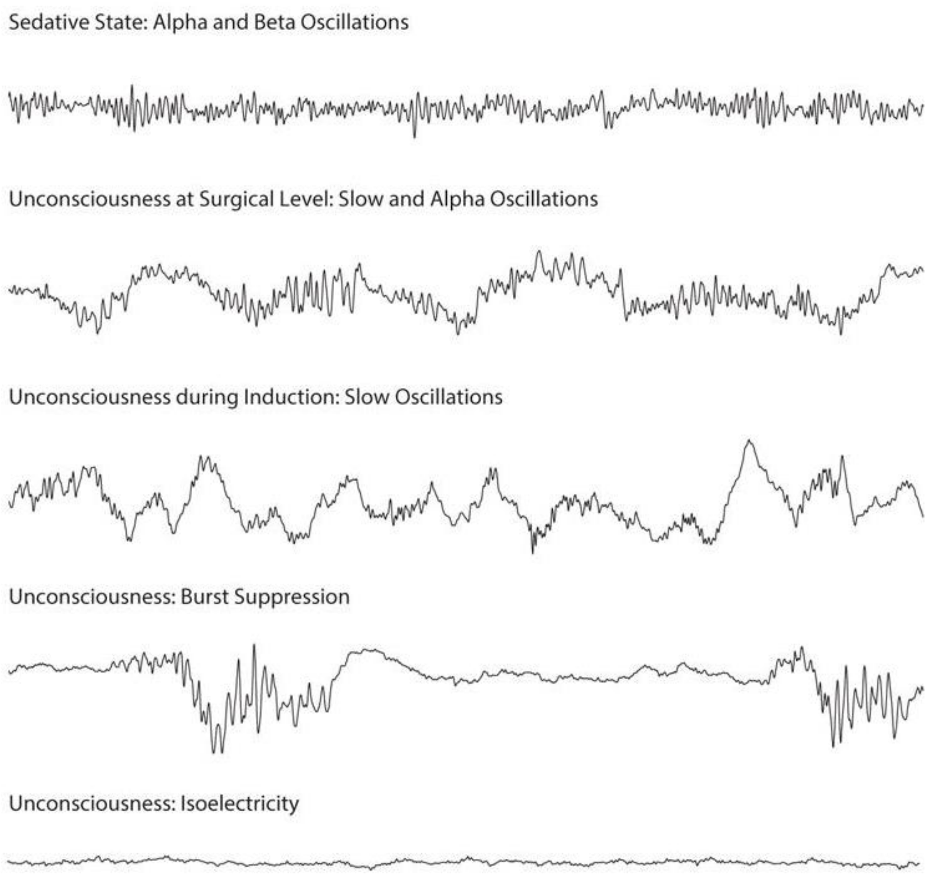


Figure 2. Examples of neural oscillations. Includes comparison of burst suppression to typical surgical sedation brain dynamics. Image courtesy of Purdon et al., 2015.[10]

Burst suppression has been found to correlate with high doses and prolonged exposure to GABAergic anesthesia.[21] This pattern of EEG waveforms is important to note clinically during surgery, as it is indicative of a highly suppressed central nervous system and has been correlated with an increase in post-operative cognitive declines, such as POD, causing an increased hospital stay, post-operation.[22] Thus, analyzing recovery biomarkers for correlations to burst suppression may offer an insight into future tools for recovery prediction. This is especially true for elderly patients, who tend to be at a higher risk for experiencing burst suppression after anesthetic exposure.[19]

Due to the nature of EEG's high temporal resolutions, EEG has become an important tool for identifying biomarkers suggesting early onset of neurological diseases. Early diagnosis is extremely vital for slowing the progression of diseases by early medical intervention. Some of the neurocognitive diseases previously studies that EEG has been effective in finding biomarkers of early onset include Alzheimer's disease, dementia, and Parkinson's disease.[23,24,25] The versatility in EEG is a feature that has allowed for widespread implementation in neurocognitive assessments and will continue to do so as researcher further explore biomarkers associated with post-operative delirium. Some current studies observing delta waves in the post-operative stage of cardiac surgery have begun to use eyes-closed EEG as a predictive tool for delirium with significant success.[26] The ability to have a quantitative measurement to define delirium may help with differing opinions on the patient care team, as well as provide a tool for insurance to define certain treatments as nessecary. and thus covered, for patients experiencing delirium.

This thesis will further explore if EEG can indicate lengths of hospital stays and post-operative complications in future applications. Much prior research has focused on EEG patterns in invasive, needle-based EEG monitoring during operations. Invasive EEG requires an extensively trained technician present through the full duration of the case. Additionally, is often difficult in certain cases where rotation of patient's position is necessary.

This thesis will focus on non-invasive sticker EEG monitoring rather than invasive. Non-invasive EEG provides a more cost-effective monitoring option, that opens EEG monitoring to all surgical procedures in hospitals with less resources. Non-invasive EEG also provides an effective quantitative analysis, showing exact proportions of oscillation states through-out the surgical procedure. Thus, it is a more predictive analysis than a qualitative measure such as consciousness might provide. The results of this study will encourage healthcare professionals to recognize the benefits of using EEG in all surgical procedures as well as look towards future studies that may implement EEG benefits withing the post-anesthesia care unit (PACU) to minimize risks and maximize recovery drug effectiveness.

Clinical Neurocognitive Measures

Unconsciousness under general anesthesia is often referred to as 'sleep', yet the arousal from chemical sedation and sleep are drastically different. Waking from sleep produces a transitional state prior to returning to full neurocognitive baseline referred to as sleep inertia. In sleep inertia, an individual experiences lower levels of arousal to stimuli that has been found to last anywhere from one minute to four hours.[27] In comparison, patients waking from anesthesia can take anywhere from within the first hour post-operation to days after the surgery to reach a full cognitive recovery. Within this recovery period, patients experience a multitude of symptoms produced from the chemical manipulation of anesthesia. These differ from the those typically produced in melatonin induced sleep. Explanations for this may include temporal indications of specific neurological networks that take longer to re-establish connections after anesthetic blockade. The essential differences between sleep recovery and anesthetic recovery still have yet to be fully uncovered.

EEG has been used to identify biomarkers of both naturally occurring sleep and anesthetic induced sleep by assessing brainwave amplitude and power on a spectrogram. EEG studies focused on melatonin, the main sleep hormone, showed that when melatonin was injected intravenously at dosages comparative to intraoperative propofol, melatonin produce similar power frequencies.[28] Alongside this, we know in naturally occuring sleep, similar slow delta waves seen in intraoperative EEG are present. However, recovery from anesthetics coincides with longer delays in cognitive recovery and slower wake-up times, indicating further physiological differences. The largest difference between EEG in naturally occuring sleep and anesthetic induced sleep is the presence of alpha waves, which are not apparent during sleep unless in the rapid eye movement (REM) stages.[29] These alpha oscillations are likely due to the GABAergic drugs discussed earlier such as propofol. While propofol lengthens GABA's effects, it also cause a rhythmic increase in thalamic activity that produces alpha waves in the normal waking state.[30] This neurochemical effect, along with many others occuring at the molecular level of anesthetics, likely contribute to neurocognitive delays in the post-operative recovery time.

In perioperative care units, including the PACU and the Center for Peri-anesthesia Care (CPC), it is standard practice for medical professionals to assess simple neurocognitive measure each time a patient is approached, such as the alert and oriented scale. However, as more studies continue to assess recovery in post-operative patients, results have found "alert and oriented x3" to miss a significant number of cognitive impairments.[31] Thus, more specific scaling is required when assessing post-operative neurocognitive status. Evaluations such as the Richmond agitation-sedation scale, also known as RASS and reaction time via auditory psychomotor vigilance testing (aPVT) will be utilized in this study.

Richmond Agitation-Sedation Scale

The RASS scale is referred to as a more in-depth assessment of sedation, as it assesses eye contact, agitation, vocal responses, and drowsiness, as compared to other evaluation methods which rely primarily on drowsiness alone.[32] The scale has been found as a valid measure of sedation for ICU patients (both with and without ventilation) in determination of medication dosages in multiple studies.[32,33] Validity measures to assess RASS have included both comparative analysis to various sedation scales and nurse medication evaluations. Nurses in all studies agreed the scale was not complex in administration and recall, suggesting easy integration into standard medical care practices. This scale has been studied as a value of sedation for surgical intensive care unit (ICU) patients and is now being used as a value of recovery times within peri-operative units to evaluate if a patient is ready for discharge to the next step of care (home for outpatient surgeries, a patient room on a surgical floor for inpatient surgeries). Level of consciousness is a large determinate of not only how a patient is recovering.

Auditory Psychomotor Vigilance Testing

Sustained attention and vigilance have been shown in studies to be predictors of neurocognitive function in brains of patients over the age of 70.[34] Further, when functional magnetic resonance imaging (fMRI) testing was applied to reaction time tests for both older adults and younger populations, older adults showed greater activity in the frontoparietal attentional areas when reaction times were longer.[35] Applying this to the implications of post-operative recovery suggest that attention and vigilance may be predictive factors of the recovery timeline and may show importance differences in recovery with age. There have been a wide range of tasks to measure these two values via reaction time, but these tasks often involved intense physical activity, such as standing and grasping falling objects, or avoidance type jumping. These tasks would be too physically demanding for patients directly out of surgery. Thus, in order to use attention and vigilance as a valid neurocognitive measure of surgical recovery, a reaction time test should be developed in which the patient can show an accurate evaluation of their response time, while abiding by to the surgeon's post-surgical rest regime.

This study will evaluate reaction time through a test known as aPVT, an auditory reaction time instrument, with software developed within the Patrick Purdon laboratory.[21] Within this task, patient will, through headphones, hear either their name or a buzz, and be asked to respond in a timely manner to this stimulus. Thus, we will be able to measure the level of attention and vigilance through a task where the patient may remain sedentary, thus avoiding conflicts with their recovery regime. We expect to see a parallel between aPVT performance and neurocognitive recovery in post-surgical patients, with a greater reaction time associated with older age.

Aims

The aim of this study is to assess the correlations between neurocognitive recovery measures of attention and vigilance to brain dynamics. Two specific aims will be analyzed to target specific indications of recovery. Firstly, non-invasive EEG will be utilized in this study to determine the association between intraoperative burst suppression and neurocognitive recovery. Secondly, post-surgical testing will evaluate the neurophysiological markers of performance in the auditory and reaction pathways.

METHODS

Subjects

A total of 190 patients were initially enrolled in the study. All subjects were 18 years or older, undergoing general anesthesia during a surgical procedure at Massachusetts General Hospital between September 2021 and November 2022. For this study, general anesthesia is defined as the reversible use of anesthetic drugs to produce a temporary loss of consciousness and movement, analgesia, and amnesia. Patients receiving only local anesthetics were excluded. Patients were approached on the day of surgical intervention, 2 hours prior to their scheduled operation. All patients signed a consent form prior to any pre-operative testing and were each given a copy of the consent form to take home. Patients were further informed that if they wished to unenroll from the study at any point through-out, they may do so without change to their medical care.

The inclusion criteria were: 1) patient must be a fluent English speaker 2) have no visual, hearing, or language impairments 3) have an American Society of Anesthesiologists (ASA) physical status classification of III or below. The following table outlines ASA status recommendations.

ASA Physical Status Classification	**Definition of Patient Status**	**Anesthesia Complication/Risk Predictions**
ASA I	Patient that is healthy	Low risk anesthetic complications

ASA II	Patient with mild condition	Mild risk of anesthetic complications
ASA III	Patient with severe condition	Mild risk of anesthetic complications
ASA IV	Patient with severe condition that threatens life	High risk of anesthetic complications
ASA V	Patient in critical condition, not expected to survive without surgery	Extreme risk of anesthetic complications
ASA VI	Patient that is pronounced brain-dead, undergoing surgery for organ removal	Null risk of anesthetic complication

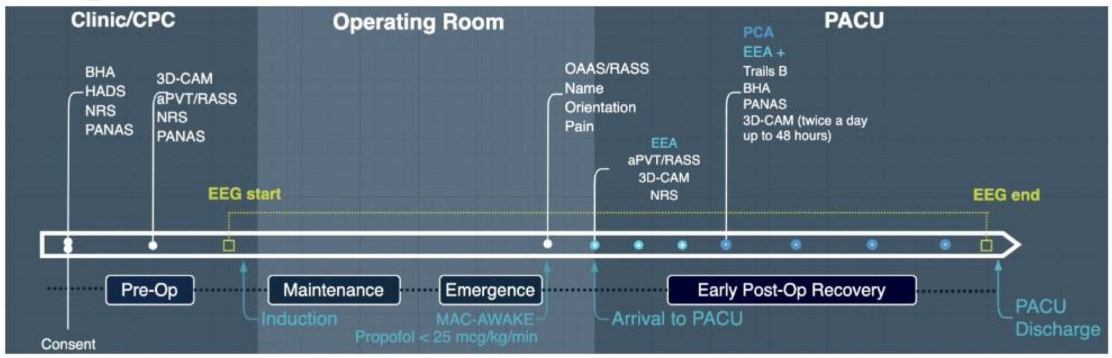
Table 1. ASA Physical Status Classification Guidelines[36]

The final exclusion criteria were 4) planned post-operative ICU stay and 5) unplanned ICU admission (these patients were enrolled prior but excluded upon ICU admission). The exclusion of ICU patients to allow for critical care treatments without study interference. Only patients transported to the PACU were included.

Reasons for early patient unenrollment include unenrollment for anxiety, EEG sticker irritation/reapplication, surgery cancellation, anesthetic change to local only, impairments causing insufficiency to complete tasks, and clinical team requests to unenroll patient. Unenrollment due to surgical complications included surgical delays and patient needing ICU care post-operatively.

Protocol

Pre-Operation Protocol



BHA: Brain Health Assessment; HADS: Hospital Anxiety and Depression Scale; NPRS: Numeric Rating Scale to asses pain ; 3D-CAM: 3-minute Diagnostic Assessment for Delirium using the Confusion Assessment Method; aPVT: Auditory Psychomotor Vigilance Test; RASS: Richmond Agitation and Sedation Scale; Trails A & B: Trail; making test part A & B; Category Fluency; PANAS: Positive And Negative Affect Schedule; EEG: Electroencephalogram standard anesthesia clinical monitoring (SedLine®).

Figure 3. Timeline of study protocol as approved by the IRB. The only variables of consideration in this paper are EEG, aPVT, RASS, and OAA/S. [37]

The Institution Review Board (IRB) approved the protocol displayed in Figure 3, No. 2020P003234, on December 18th, 2020. All researcher staff collecting data were trained by an experienced neuropsychologist in the full cognitive battery per hospital guidelines. A full cognitive assessment was given in the two hours prior to the operation to gather a baseline for each patient's neurocognitive status. For this thesis, only RASS, and aPVT will be considered. Each patient underwent these tests after forehead placement of an EEG monitor. The EEG monitoring sticker consisted of 5 electrodes, one in the central zone, above the brow bone for reference, three recording electrodes on the frontal bone, and two recording electrodes over the temple region on either side. The EEG sticker was connected to a Masimo SEDLine® monitor for data capture.

Each electrode was checked for impedance. A green feedback on the SEDLine represented an impedance under 15 kilo-ohms, which was the gold standard for this study. A yellow feedback for a given sticker was also acceptable, under 25 kilo-ohms. A red sticker over 25 kilo-ohms was under the standards for this study and indicated to the researcher to gauge if a better connection was possible through adjustments, or if the sticker needed to be replaced. A gray or blue electrode feedback was presented when the connection to the SEDLine was unable to be established, or the electrode was non-functional. In either of the latter scenarios, the EEG sticker would be replaced with a new one to ensure proper connection and thus quality EEG data recordings. Upon every data collection event, the SEDLine was marked with a timestamp.

After EEG placement was complete, aPVT testing for the pre-operative baseline occurred. Prior to the patient encounter, MATLab software was used to create sound files of the patient's first name.[38] Patients were given headphones and a mouse and instructed to click the mouse when they hear their name or a monotone hum. The test lasts for approximately 3 minutes on average, on occasion being stopped after 1 minute due to hospital staff workflow. Using neurobehavioral systems presentation, when the patient correctly clicked upon presentation of their name or a hum stimulus, a green box would appear to indicate a positive hit. If the patient clicked the mouse when no stimuli was presented, a black box would appear to indicate a false hit. If the patient did not click the mouse when a stimulus was presented, a red box would appear to indicate a miss. The aPVT software collected reaction time as the milliseconds between signal presence and mouse clicks. Data of reaction time following each stimuli presentation, number of false hits and misses were recorded as well as time stamped. EEG SEDLine was time stamped at the start as well as the conclusion of the testing. False hits and misses were added together in analysis in order to evaluate accuracy as a factor of percentage missed. Percentage missed was the total of the sum of false alarms and misses divided by the total number of attempts ('trials').

EEG was stopped prior to the patient entering the operating room, with a goal collection of at least forty-five minutes of EEG data. If the surgery were delayed, EEG data would be stopped prior to entering the operating room while still in the CPC, as long as forty-five minutes was already reached. However, the EEG sticker always remained on the patient, thus utilizing the same electrode placement for the duration of their surgery day.

Operating Room Protocol

Once the patient was moved into the operating room, a new EEG recording began. Four timestamps were completed during induction: induction start, propofol start, loss of consciousness, and intubation. Induction start is recorded during the first IV medication injection, propofol start is recorded at the first bolus push of propofol, loss of consciousness is recorded at the time of eye taping, and intubation is recorded with the tracheal introducer guide tube extraction. EEG is recorded for the totality of the operation and anesthetic regimes are recorded via the anesthetists' Epic record.[39] At the conclusion of surgery, four event times are collected: Gas anesthesia MAC falls at or below 0.2, all anesthesia is turned off, observer's assessment agitation/sedation scale (OAA/S) reaches a value of 0.2 or greater, and extubation.[40]

After extubation and a clear from the anesthesiologists, researchers assessed OAA/S value utilizing the guidelines in Table 2.[40] The researchers' protocol was to call the patient's last name in a normal tone of voice twice and wait for a response. If no response was gathered, they would then repeat in a louder voice. If no response was gathers researchers would gently shake the patient and call their name in order to gather a response. Questions asked were "what is your first name?" and "where are you right now?". Correct answers for location included hospital, surgery, operating room and "MGH" ("Mass Gen" was counted as correct). The evaluation was performed approximately once every minute after extubation until an OAA/S of 2 was reached or until the patient was moved out of the operating room. The patient was only required to answer these two questions for OAA/S to be assessed.

Assessment Categories				Composite score level
Responsiveness	**Speech**	**Facial Expression**	**Eyes**	
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	**5 (alert)**
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	**4**
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and mild ptosis (half the eye or more)	**3**
Responds only after mild prodding or shaking	Few recognizable words	-	-	**2**
Does not respond to mild prodding or shaking	-	-	-	**1 (deep sleep)**

Table 2. Observer's Assessment Agitation/Sedation (OAA/S) Scale.[40]

If a response on the OAA/S scale was achieved, patients would then be asked to verbally inform researchers of their current state of pain before leaving the operating room on a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable. RASS score would be evaluated after responses. If the patient had no response to any of the questions after awakening from surgery, the last attempt to answer the questions would be time marked and RASS would be evaluated. Event time was also recorded as the patient left the operating room and arrived at the PACU. Once arrived at the PACU a new EEG recording would begin for emergence and post-operation.

Post-Anesthesia Care Unit Protocol

Per protocol, within the first hour of emergence, RASS and aPVT were performed in fifteen-minute intervals starting from the last attempt to answer the patients name, location, and pain level. However, it was vital that discretion be given to evaluate whether the patient was in too much pain or RASS score was too low to complete the testing, in order to prioritize proper surgical recovery. Workflow of anesthesiologist, nurses, and surgeons was also prioritized during the recovery stage, permitting follow-ups to pause the neurocognitive testing.

RASS was determined in the first 5 minutes of cognitive testing. Each researcher was trained to score RASS based on the guidelines presented in Table 3. RASS scores in this study are used as an indicator of recovery. A score of -1 or greater in this study will correspond to a neurocognitive recovery due to lack of sedation. The discharging criteria for patient to leave the PACU requires that, in the Aldrete scoring system, they reach phase 1 early recovery.[36] In practice, the scoring of this system is equivalent to a RASS score of -1 in terms of general patient consciousness, and thus we will define a RASS score of -1 as a post-operation recovery score for the PACU.

Criteria	Definition	Points
Combative	Overtly combative, violent, immediate danger to staff	+4
Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	+3
Agitated	Frequent non-purposeful movement, fights ventilator	+2
Restless	Anxious but movements not aggressive vigorous	+1
Alert and calm		0
Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)	-1
Light sedation	Briefly awakens with eye contact to voice (<10 seconds)	-2
Moderate sedation	Movement or eye opening to voice (but no eye contact)	-3
Deep sedation	No response to voice, but movement or eye opening to physical stimulation	-4
Unarousable	No response to voice or physical stimulation	-5

Table 3. Richmond Agitation-Sedation Scale. Table courtesy of Sessler et al., 2002.[32]

After the first hour of emergence, post-operative testing with the same regime was performed every hour on the hour, for either three hours or until the patient was moved out of the PACU, based on which event occurred first. I participated in all patient recruitment, consenting, and data collection.

Analysis

Data was collected and managed via Epic and REDCap electronic data capture tools hosted at Massachusetts General Hospital.[39,41] Analysis was conducted using RStudio software.[42] Reaction times for each stage of aPVT testing were averaged and percentage missed calculated as a factor of all trials in each occurrence. Shapiro and Wilcoxon sign-ranked tests were conducted to analyze if emergence and/or post-operative values showed significant deviations from baseline for any of the neurocognitive tests.[43,44] This was visualized via QQPlots.[45] The differences between pre-op and PACU values for each individual patient were determined and analyzed. Intraoperative EEG was analyzed for presence of burst suppression during the operation as a proportion of total surgical time.

Multiple linear regression models were used to determine if reaction times were accurate predictors PACU surgical recovery time with accountability of possible confounding variables. Multiple linear regression models were also used to determine the predictive association between intraoperative burst suppression occurrence and reaction time. For all models, likelihood ratio tests were also conducted in order to determine the statistical s of each relationship present. I completed all data analysis.

RESULTS

Patient Population and Demographics

An initial group of 145 patients were included in study enrollment. Patients were only included if aPVT data was collected in both the pre-operation stages and after initial emergence in the PACU, in order to control variables for proper baseline assessment. Approximately 30 patients lacked an intraoperative EEG file and were thus excluded from the population group analyzed for burst suppression. The final population is represented in Figure 4 below.

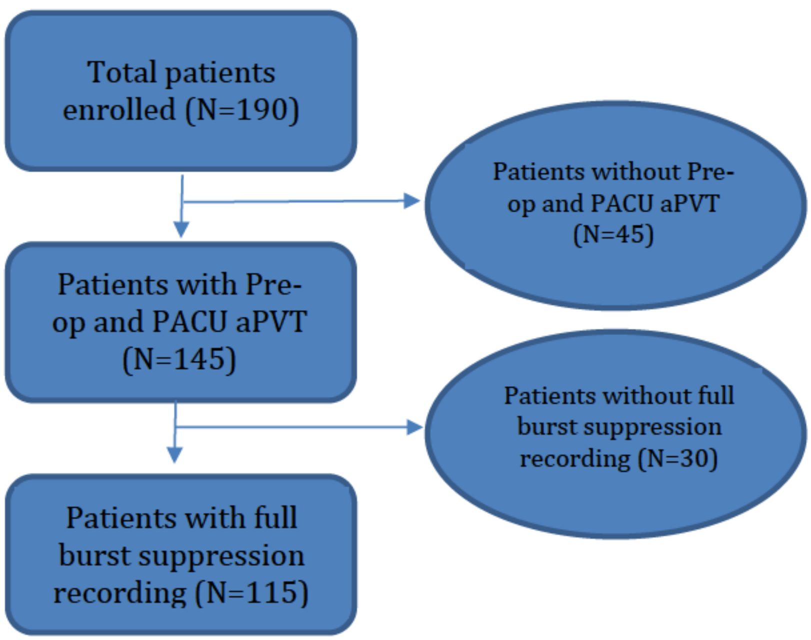


Figure 4. Consort Chart for Patient Population

The final population consists of 77 females and 68 males, all over the age of 18. At intake nurses collected patient race and reported the information to Epic records, which were pulled for analysis. 125 patients identified as white, 5 patients as black, 6 patients as Asian, 6 patients as other, 2 patients declined to answer, and 1 patient did not have a race recorded in their medical records. ASA status was assessed by the anesthesiologists and reported in Epic records as well. The majority of patients had an ASA status of 3 (N=69, 48%) or 2 (N=69, 48%), with only 2 patients having an ASA status of 1 (N=2); 6 patients did not have an ASA status in their medical record. In terms of handedness, 4 patients were ambidextrous, 121 were right-handed, and 15 patients were left-handed. The most common type of surgery was colorectal, making up 59% of the procedures performed. Age ranges from 19-92 years old, as shown in Figure 5. below, with a mean of 57 (± 15) years old.

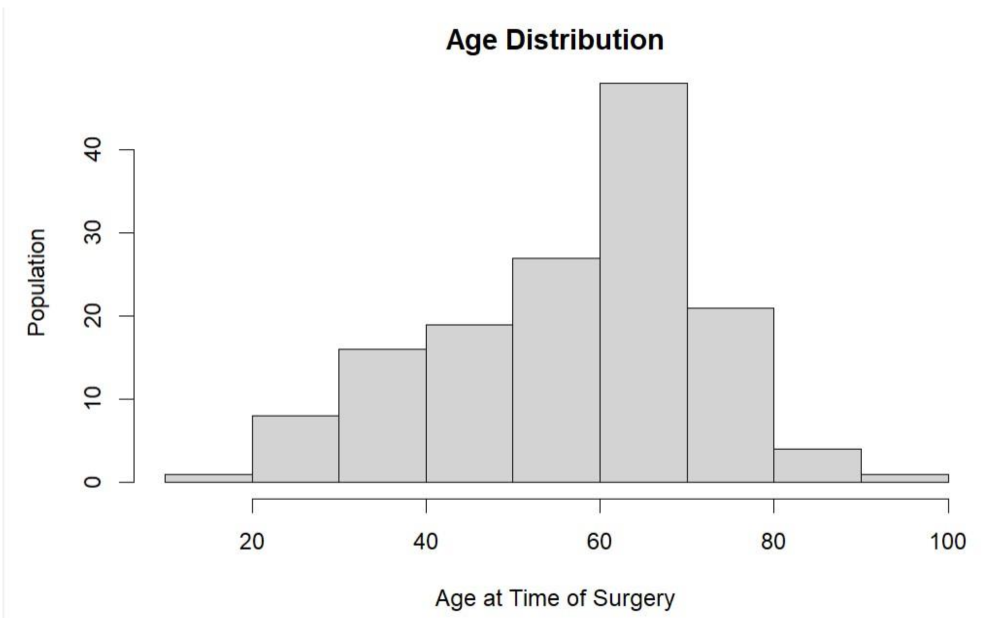


Figure 5. Age Distribution for total patient population.

It is important to note the right skewed distribution of ages presented in our population. The largest population age group in this study is 60-70 years old (N=63), a common occurrence in hospitals around the country. Ages 50 and older, the ages in which neurocognitive decline tends to begin, correspond to 70% of our study population. As this population group ages, it is expected that this right skewed distribution continues to increase nationwide.

Year of education had a wide range present, from a minimal length of 6 years to a maximal length of 25 years. Education years counted from 1st grade (primary education) to completion of doctoral degrees. Undergraduate education counted for 3 years if no degree was received, and 4 years if a degree was achieved. The two largest educational groups in our population were completion of high school, 12 years (N= 26), and completion of undergraduate education, 16 years (N=47).

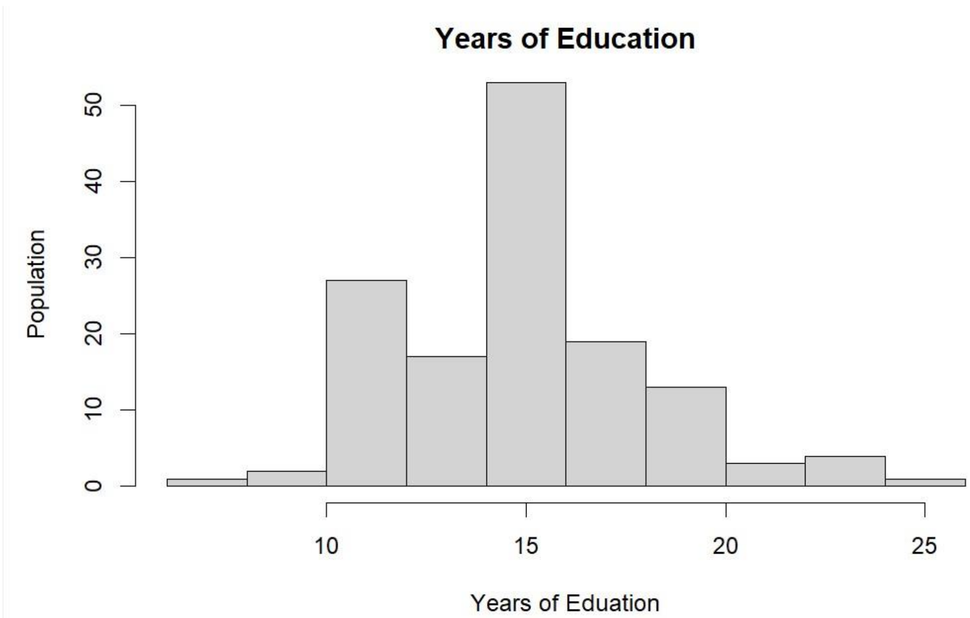


Figure 6. Distribution of Years of Education for patient population.

It is important to notice the high level of education in our study population. This study was conducted at Massachusetts's General Hospital, a hospital located in Boston, Massachusetts. This city is largely a collegiate city, and according to recent analysis, in a state ranking fifth best in the country for primary education.[47] Only 4 patients in our study did not complete primary education, eliciting the conclusion that the education status of the community studied is skewed to the right.

Patient Population Demographics

	aPVT	aPVT + Burst Suppression
n	145	115
Age	57 ± 15	58 ± 15
Sex (Female)	77	58
Years of Education	16 ± 3	15 ± 3

Table 4. Values for continuous variables are means followed by standard deviation.

Auditory Psychomotor Vigilance Testing

Reaction time and accuracy was assessed in both pre-operative, emergence, and post-operative stages. Only one pre-operative aPVT was collected for each subject for baseline measures. After emergence, multiple occurrences of aPVT were collected at variable time points. The lowest accuracy aPVT and longest reaction time (RT) aPVT data points were assessed and compared to baseline in order to account for the heaviest effects of anesthesia.

Baseline aPVT RT in pre-op had a range between 358.18 milliseconds (ms) and 1502.81 ms, with an average time of all subjects at 768.70 ms (SD= ±257.11 ms). Out of 145 patients, the majority (N=118) had baseline RT under 1000 ms. Two subjects in the pre-op stage had a reaction time greater than 1500 ms.

In PACU assessments, the range for all subject reaction times was from 509.11 ms to 3253.00 ms with a total population average time of 1112.14 ms (SD= ±424.17 ms). One subject, MGHOE051 was an outlier, with a max average RT of 3253 ms in their PACU aPVT assessments, a 2433.129 ms increase from pre-op assessment. Three further outliers had max average RTs greater than 2000 ms. Twenty-seven total subjects had RTs greater than 1500 ms.

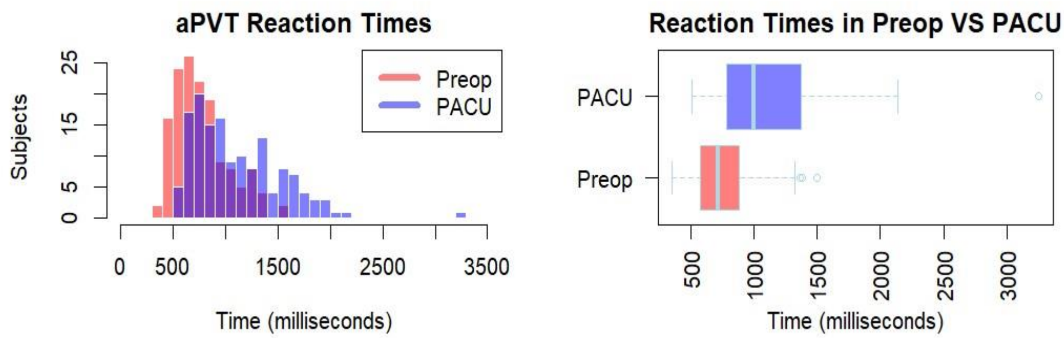


Figure 7. aPVT RT in Pre-op and PACU. PACU values represent the longest RT for each subject. On the left, a histogram represents the difference between pre-op and PACU, while on the right a boxplot highlights the difference in mean reaction time.

Accuracy was determined as a percentage of the misses and false alarms in the total number of trials conducted. In the pre-op stages, the vast majority of subjects (N=105) percentage-missed fell between 0% to 5%. Eighty-four patients had no misses in their baseline. Only five subjects had a percentage missed greater than 30%. The average percentage missed in the pre-op stages for the total patient population was calculated to 5.03% (SD = ±10.22%). In the PACU assessments, subjects with a percentage-missed between 0% and 5% dropped to thirty-two. Only twelve patients had no misses in their PACU assessments. The majority of patients (N=84) had a percentage missed between 0% and 30%. The average percentage missed in the PACU stages for the total patient population was calculated to 32.42% (SD= ±30.71%), a 27.39% increase from the average in the pre-op stages. In further comparison to the pre-op stage where only five subjects had a percentage missed greater than 30%, 62 subjects in the PACU stages had a percentage missed over 30%.

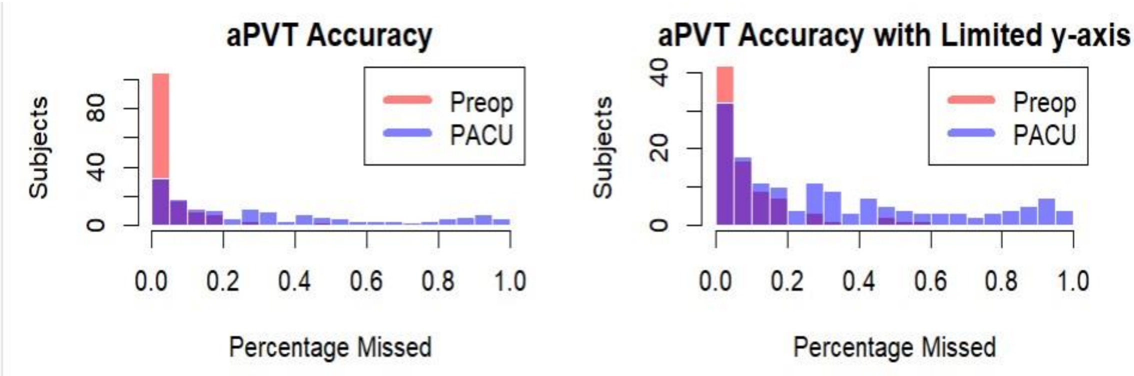


Figure 8. aPVT Accuracy in Pre-op and PACU assessments by function of percentage missed. PACU values represent the lowest accuracy measurement for each subject. The left plot has total patient population, while the right figure expands the y-axis of subject at N=40 to allow for clarity of pre-op to post-op subject numbers in each category of percentage missed. Purple coloring indicates an overlap of pre-op and PACU values.

Group Distribution Normalcy

Both reaction time and percentage missed (accuracy) were used in the data analysis as measures of attention and vigilance. Analysis was done in both regards to the population as a whole and individuals. For individuals, the baseline values were subtracted from the PACU values in order to assess the change due to anesthetics. In order to do this, both groups of data were first assessed for normalcy. As Figure 7 and 8 show, a normal bell curve is not presented in the distributions for either reaction time or percentage missed. To ensure non-normalcy of data distribution, two methods of assessment were conducted to determine the statistical data distribution characteristics. A Shapiro test was run for all four sets of data (pre-op RT and percentage missed, PACU RT and percentage missed).

Shapiro Test Results

Group	W	p-value
Pre-operative Reaction Time	0.92763	9.862×10^{-7}
Pre-operative % Missed	0.55053	2.2×10^{-16}
PACU Reaction Time	0.90667	4.866×10^{-8}
PACU % Missed	0.86282	2.765×10^{-10}
Significant p-value = 0.05		

Table 5. Shapiro test results to determine normalcy of data groups.

Within the Shapiro test, a non-significant result suggests normalcy of data distribution. In all four groups in Table 5, the p-value was significant, showing the distribution of the data is a non-parametric. For a second confirmation of this distribution characteristic, QQPlots were created for each group.

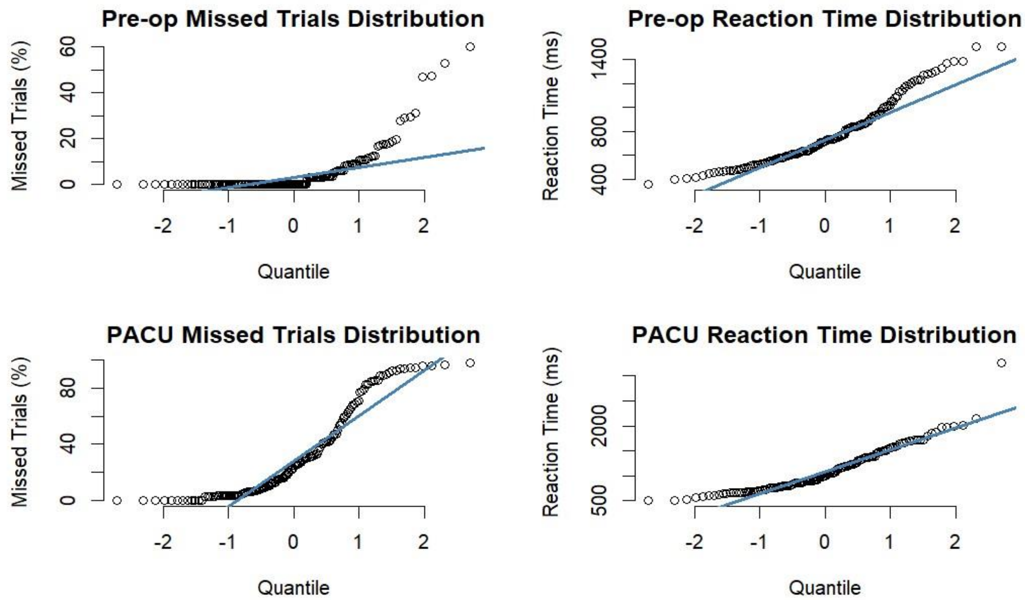


Figure 9. Data groups plotted against a normalcy line in distributed quantiles.

QQPlots are plotted in theoretical quantiles, in which at quantile 1, 75% of the data in the group falls below the given value; for example, in reaction time, 75% of the data should fall below 1500 ms.[45] The deviance from both normal distributed shown in Figure 9 suggests visually that the data groups are skewed and not normally distributed.

Distinction in Group Distributions

With non-parametric data groups, a Wilcoxon signed-rank test was conducted in order to determine if the means of pre-op to PACU reaction time and accuracy values differed significantly. Results are shown in Table 6 below.

Wilcoxon Signed-Rank Test Results

Group	Pre-op Mean	PACU Mean	W	p-value
Reaction Time	768.70 ms ±257.11	1112.14 ms ±424.17	16104	4.876×10^{-15}
Accuracy	5.03% ±10.22	32.42% ±30.71	17805	2.2×10^{-16}

Significant p-value = 0.05

Table 6. Wilcoxon Signed-Rank Test results of mean differences between data groups.

The results of both reaction time and accuracy show a significant difference between the pre-operative and PACU data groups, indicating that the data sets are non-identical and the means are significantly different values.

To determine if the difference was seen in individual patients as compared to the prior analysis in which the difference was from the entire population's data, each patients pre-operative RT and percentage missed were subtracted from the PACU values. Some patients did have improvements in the PACU, which were represented as a negative value in Figure 10 below.

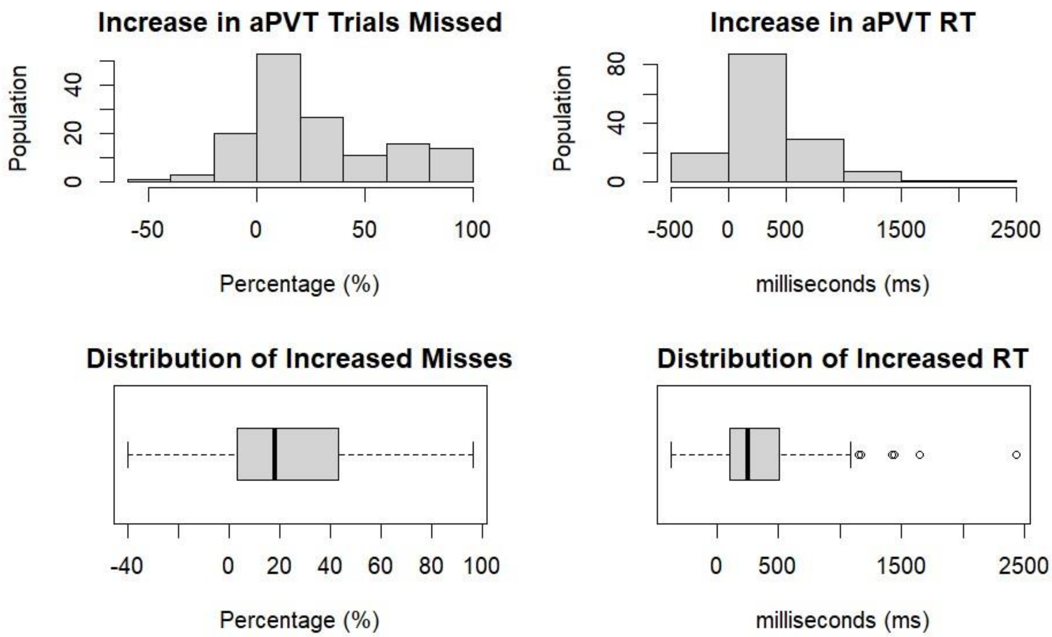


Figure 10. Distribution of aPVT accuracy and RT differences in each individual patient.

The maximum change in accuracy from pre-op to PACU was 96.30%. Ten patients had no change at all. The majority of patients had a change of 40.00% in either direction (N=100). In the positive direction, 41 patients missed between 40.00% to 96.30% more aPVT trials. The mean change in accuracy was 27.39%. The maximum change in reaction time from pre-op to PACU was an increase of 2433.13 ms, however this was an extreme outlier. All other increases were below 2000.00 ms. Thirty-seven patients had an increase between 520.00 ms to 1642.66 ms. The majority of patient (N=87) had an increase reaction time between 10.00 ms to 500.00 ms. The mean change in reaction time was 343.44 ms.

Richmond Agitation-Sedation Scale

RASS Scores were assessed from emergence 1, occuring 15 minutes after surgery, for every 15 minutes until the first hour of recovery in the PACU. Once an hour was reached, RASS score was only assessed at hour one, hour two, and hour 3 after emergence. A RASS score of -1 indicated sustained awakening and was corresponded to positive recovery. Figure 11 shows the distribution of time to reach -1 for all subjects.

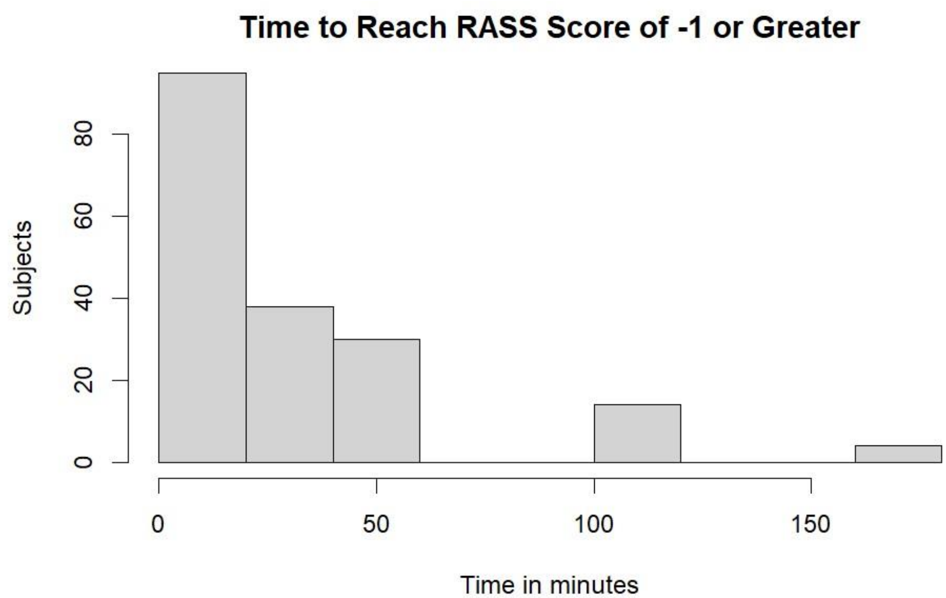


Figure 11. Time for subjects to reach RASS score of -1 or greater in minutes after initial operating room emergence.

In the current study population, the shortest time to achieve RASS score after initial operating room emergence was 15 minutes, and the longest time was 180 minutes, three hours after initial operating room emergence. One subjects had the longest recovery time of 180 minutes. An additional two patients did not reach RASS values of -1 or greater during the testing period. The majority of patients reached recovery values of RASS in the first 15 minutes after initial emergence (N=82). RASS recovery within the first hour (60 minutes) was observed in 92.41% of the population. The average time to

RASS recovery for the total subject population was calculated to be 29.59 minutes (SD = ±28.29 minutes).

Burst Suppression

Intraoperative files were pulled for 115 patients for EEG analysis. EEG was analyzed in time sections, with each section coding for occurrence of burst suppression (1) or no burst suppression (0). Time spent in burst suppression was calculated as a sum of burst suppression occurrences over the total time sections of the surgery. Thus, the results presented here are percentage of surgical EEG recording that each patient showed occurrence of burst suppression.

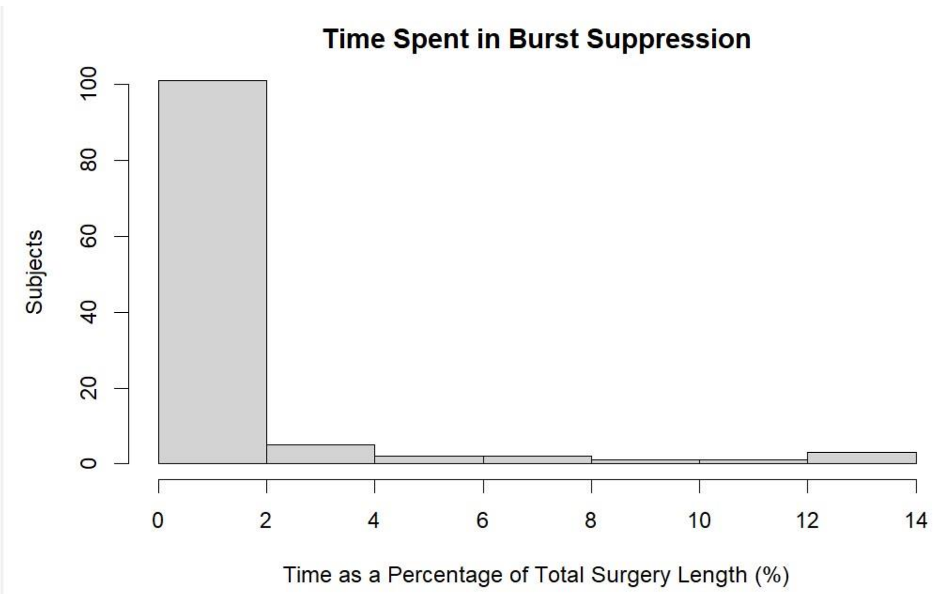


Figure 12. Time spent in burst suppression expressed as a percentage of total surgical time.

A prolonged occurrence of burst suppression was defined as equal to or greater than 5% of total recording time. Prolonged burst suppression was found in 7% of patients (N=8), with burst suppression time range from 0% to 13.85% of complete time elapsed as shown in Figure 12. Burst suppression occurrence was 0% in 25 patients. The majority (N=98) of patients spent less than 1% of total surgical time in burst suppression.

Association of Burst Suppression. aPVT, and RASS

A total of six models were run in this analysis to fully assess our aims. The first model ran analyzed the linear regression between RT and RASS to test the significance of aPVT performance. RT association to RASS recovery time was found to be significant with a coefficient of 0.019 (p=0.0006).

The second through fourth models were run to analyze if aPVT percentage missed and age were confounding variables. Reaction time coefficient with percentage missed was changed and found to be significant with a coefficient of 0.014 (p=0.0443). Percentage missed changed the coefficient by less than 10% (change was equivalent to 7%), suggesting that the interaction is not significant and that percentage missed should be left out of the model. Introduction of age into the model also changed the coefficient, this time at a 20% change from 0.015 to 0.022 (p=0.000111), suggesting that age may be a confounding variable. A likelihood ratio test was run for age as a confounding factor of RT association with RASS which was significant (p=0.04421) indicating that age should be kept in the model. The fourth model introduced age and RT as an interaction variable but was found to be insignificant (p=0.2099) and thus the association of RT to age does not change with increasing age in our model. Overall, the final reported result for RT coefficient is 0.022 (p=0.000111), or 22 minutes of RASS recovery time for every 1000 milliseconds in reaction time.

The fifth and sixth model were run to determine the association between burst suppression occurrence (BSO) and aPVT performance. The fifth model ran association of burst suppression to the maximum RT in the PACU. The association was found to be non-significant (p=0.497). To take a full scope approach to performance measures, the sixth model was run to determine association of burst suppression occurrence to each patient's RT difference value (difference of increase or decrease in RT between PACU and pre-op). This model was also found to be insignificant (p=0.758), suggesting that in this study there was no association between reaction time and burst suppression. A final, seventh, model was run to account for any correlations between the increased education of our population and low occurrence of burst suppression. Years of education was found to be insignificantly associated with burst suppression (p=0.0501) suggesting no relationship in the present population.

Multiple Regression Model Results

Outcomes	*Fixed Coefficient Estimate*	*SE*	*tstat*	*p-value*
RT	0.022	0.006	3.977	0.000111
Misses	0.128	0.093	1.383	0.1688
Age	-0.304	0.151	-2.005	0.046886
RT*Age	-0.0005	0.0004	-1.260	0.2099
BSO (with RT Time)	4.136	13.382	0.0309	0.758
BSO (with RT Difference)	7.998	11.734	0.682	0.497
Education Years	0.158	0.797	1.980	0.0501

Significant p-value = 0.05

Table 7. Outcomes of Multiple Regression Models for Brain Dynamics & Performance Measures.

DISCUSSION

As we look forward to the future of surgery, it is important that we find cohesive markers of recovery to efficiently ensure patients have the level of recovery support necessary in the post-surgical timeframe. Being able to plan presumptively as well as have objective measures adjust the care plan will allow for more efficient streamlining in the PACU. As we consider the relevance of current rises in ambulatory surgeries and the aging population, we can see the importance of research into anesthesia effects on the brain and recovery.

Significant of Reaction Pathway Associations

One of the main goals of this study was to evaluate the neurophysiological markers of performance in the auditory and reaction pathways. Reaction time via auditory psychomotor vigilance testing is shown to have significant associations with RASS recovery time and is shown to be influenced consistently by age. This form of testing is an adequate parallel for cortical recovery from anesthetics due to its utilization of multiple communication pathways. Cortical pathways used in reaction tests utilizing in aPVT include the working memory pathways, auditory pathways, and the motor function response pathways. These various neuronal circuits allow for a widespread analysis of anesthesia's early effects, which was confirmed through our data analysis.

Anatomical and Physiological Impacts

Associating reaction time with recovery time provides insight to areas of the brain in which anesthesia has effects and which are most important for recovery. The molecular effects of anesthesia are well studied in animals that can be euthanized, yet live human models are much more difficult to pinpoint direct effects. Many of these details must be gathered through inference of associations. Our evaluation has found that reaction time has a strong association with the recovery from anesthesia, which allows us to infer that those areas associated to reaction time, and thus attention and executive function, are likely affected by general anesthesia. In particular, we know that older patients who have longer reaction times have been shown on fMRIs to have increased frontoparietal activity.[35] Long term effects of anesthesia in this population may lead to declines associated with the frontoparietal region- for example: difficulty in concentration and decision making.

Attention deficits in elderly populations are often associated with the beginning of chronic conditions such as dementia and Alzheimer's. It is an interesting correlation that animal models show linkage between exposure to sevoflurane and development of a major Alzheimer risk factor- tau phosphorylation.[17] Further studies should be conducted to determine whether general anesthesia exacerbates the development of these risk factors and the decline in the associated areas of the frontoparietal cortex. It may, instead, be found that the presence of already developed Alzheimer risk factors will increase anesthetic recovery and reaction time. Understanding of this can help to attenuate anesthetic care for elderly population and also allow for preventative care in younger populations.

Ambulatory and Elderly Surgical Populations

Along the same line of significance, our analysis found that age was shown to be an important confounding variable in the association of reaction time to RASS recovery.

While prior knowledge confirms the neurocognitive decline associated with age, the results of this thesis further highlight the need for understandings of why anesthetics have a more profound effect on the elderly. Without this knowledge it is difficult to properly adjust anesthetic care for this population to minimize negative outcomes while still ensuring the four tenants of anesthesia are met during operations. Personalizing anesthesia care for the elderly will allow for a quicker recovery and thus discharge. This will be an espically important factor for consideration in ambulatory surgeries.

The rising burden of post-surgical care costs on the healthcare system, both financially and in personnel, has led to an increase in outpatient surgery by over 10%.[48] Outpatient surgery allows patients to recover at home, and a faster discharge at the hospital eventually translates into more surgery availability in one day and more personalized care with a better patient to staff ratio. A survey conducted in 2016 by the Commonwealth Fund showed that in the United States, 32% of respondents had waited one to four months for surgery, while 12% had to wait longer than 4 months.[49] This means a patient with chronic pain from a condition such as cervical spondylosis may have to wait months in order to receive surgery to relieve the pain. In the meantime, a large number of patients, approximately 1 in 4, will receive pre-operative pain killers, specifically opioids.[50] With the current opioid epidemic resulting in a rapid increase of drug overdose deaths, it is important to focus on reducing any factors that may cause long-term exposure to opioids in any patient to prevent long term addiction and purposeful or accidental drug abuse.[51] Furthermore, the highest increase in drug deaths in recent years has been attributed to that age range of 65+.[52] Understanding how to decrease surgical recovery times, specifically for the aging brains of the elderly populations, will not only decrease exposure to pain medications in the pre-operative months, but also the post-operative months that follow.

Optimization and Standardization of Discharge Criteria

Determining a patient's ability to be discharged from the PACU units in both inpatient and outpatient surgery typically has a criteria of low sedation levels. The current use of RASS Scores and similar scales is a subjective measure of recovery, and thus the timeline in which a patient reaches this discharge criteria often changes based on the provider. This study found a significant association between RASS recovery and reaction time- approximately twenty-two minutes of RASS recovery for every one thousand ms of aPVT. This association suggests that reaction time can provide an objective measure of sedation and consciousness in the PACU that can be used to optimize patient discharge from the PACU to home recovery or long-term hospital recovery areas. The objective use of reaction time also allows for a personalized baseline for each patient, measuring their neurocognitive state to their unique normal state baselines, rather than comparing patient to patient as happens with subjective measures in the PACU.

In a scenario in which a post-anesthesia care unit is short staffed and all the beds are full, the use of an automated aPVT system could be of use. Implementation of a low-intensity, automated reaction time test with alarms set at a particular threshold could allow for PACU staff to be able to attend to patients requiring more care in the recovery, while they could avoid disturbances such as loud noises and lights in rooms that the patient is showing quick recovery. The system could also facilitate early detection of patients with delayed neurocognitive recovery, allowing for an earlier intervention from anesthesiology and rehabilitation physicians. The increased response to delayed neurocognitive recovery may minimize the risk for long-term cognitive impairments following the recovery period.

Intraoperative Burst Suppression

Another aim of this study was to determine the association between intraoperative burst suppression and neurocognitive recovery. However, it was found that burst suppression is not significantly associated with maximum reaction time in aPVT, nor an increase in reaction time. There may be multiple reasons for this, from our forms of data analysis, the anesthesiologists training, or simply a non-association of the variables.

The first thing to consider is our analysis. We viewed burst suppression as a proportion/fraction of the total surgical time. However, burst suppression is clinically viewed as a duration- how long each burst suppression occurrence lasts. This may be a more accurate tool for understanding the effects of burst suppression on post-operative neurocognitive states and may show more significance in associations. With this in mind, it is also important to note how few patient's experienced prolong burst suppression in this study. Prior studies that have utilized burst suppression for prediction of neurocognition in the post-operative stages have shown occurrences of burst suppression greater than 31 minutes.[53] This opens the discussion to the hypothesis that time may be better indicative factor of recovery time. However, this study included patients with ASA status four (60% of their study population) and five (1%) and had a majority (66%) of their study participants undergoing open cardiac surgery, suggesting not only that these patients were much sicker than our study population, but were likely also having longer operations.

In this study, burst suppression is highly minimal in all cases. The average time patients spent in burst suppression was proportionally only 1% of their surgical times. This suggests that the prior research on burst suppression has likely led to a change in anesthetic training and thus delivery. Institutions, such as Massachusetts's General Hospital put a large amount of anesthetics training into analyzing occurrences of burst suppression via EEG, as frontoparietal EEG is a common tool used in all operating room. Thus, burst suppression may not be the best indicator as its occurrence is kept minimal and thus not representative of any major changes in neurocognitive changes in the post-operation stage.

While the lack of association of burst suppression and reaction time may be due to analysis or increased physician training in EEG techniques, it is important to consider that burst suppression may not be the optimal measure for predicting post-operative neurocognitive outcomes and recovery time. Burst suppression is defined as instances of total lack of electrical activity in the brain (isoelectricity), and thus represents a depth of anesthesia above threshold for our neuronal circuitry. The first consideration for our study is that the wide-spread effects of the anesthetics at the time of burst suppression are non-specific to regions of the brain associated with reaction time and thus correlations may be minimal. In the second, the occurrence of burst suppression is a last stage phase of brain dynamics, bypassing all other phase modulations that are present on intraoperative EEGs. We know from prior studies that the effects of anesthesia produce changes at other stages, such as increased alpha power in initial induction, and later increases in gamma power.[19] These earlier stages of activity and power changes found through phase amplitude modulation may have more of a predictive factor of neurocognitive recovery. Looking at the different phases present and their associations to reaction time and recovery is an important aspect for uncovering the biomarkers of EEG predictive of recovery times. However, in this study we were unable to find any significant correlation between brain dynamics of burst suppression and reaction time.

Limitations

Population

This study was conducted at only one institution- Massachusetts's General Hospital. With this in mind, there are several limitations presented. Firstly, the population served on this surgical unit lacks wide diversity- while there were a few different ethnicities, 86% of our study population was white. From prior studies, it is known that some ethnicities metabolize anesthetic medications at varying rates, and thus the recovery time seen in this population may not be reflective of non-majority Caucasian populations.[54]

The location of the hospital may also have influenced this study, as the education rate in Massachusetts's, and even more specifically Boston, is higher than the average American city. A longer history of education may have influence on the reaction time and cognitive processing speed of populations; however, level of education was not found in our model to affect the occurrence of burst suppression. Thus, the effects may be minimal due to the resounding similarities in burst suppression presence despite differing levels of education.

The final limitation involving the population group is the sample size. While 145 is an adequately sized sample for the analysis completed in this study, the introduction of confounding variables increases the likelihood that the significant results are skewed and that p-values should be reduced by the number of these confounding variables. However, in the case of age of the reaction time to RASS recovery model, the significant p-value could be reduced by half ($p=0.0025$) and the association would still fall under significance for this model.

Anesthesia and Medications

The largest limitation of this study is the same of all anesthesia observational studies- being that it is an observational study, we are unable to control for the type of anesthetics given intraoperatively, as well as the pain medications in the PACU. Patients are commonly given strong medications in the PACU, that often cause the patients to be more heavily sedated. Thus, a patient may reach a RASS score at -1, the point of recovery, and then at the next stay dip below -1 after being given certain pain medications such as opioids. With this, some patients were unable to complete some aPVT trials due to either falling asleep or heavy sedation, both due to post-operative pain medication.

On the opposite hand, the majority of surgeries observed in this study were colorectal (59%) and thus likely received similar medications. Data collected at one institution did allow us to mostly control for difference in anesthetics training as most operating rooms had regimens for typical colorectal surgeries that they followed permitting a typical patient history. While our study is very reflective of colorectal surgeries, the results may change with a wider variety of operations being performed. For example, if this study were to include cardiovascular or neurological surgeries, which tend to have longer recovery time, the coefficient for recovery time to reaction time may change slightly or drastically. In these more meticulous types of surgeries, the length of surgical time and thus time the patient is unconcious also tends to show an increase, which may be a confounding variable in studies of these surgeries. It is important moving forwards to look not only at more various types of surgery, but also to control and analyze how the medications given can affect the results we have found here.

Equipment and Testing Protocols

The duration of this study over three years proved to be an issue for our EEG equipment. At the conclusion of this study, the EEG electrode wires within the forehead sticker began to deteriorate, and connection between the electrodes and the SEDLine became lost. The study team would replace stickers when deterioration was present, but this did lead to a short time period with an interruption in the EEG recording. The replacement of the sticker could also lead to minute placement changes which may display minuscular changed in the EEG recording, however those changes should be small enough to not affect burst suppression readings. In the operating room, there were also a few occurrences of slight stops in the EEG recordings due to the care team disconnecting the SEDLine connector in order to gain access to a patient during a code or other critical intraoperative event. In these scenarios, the care team often tried to let us know in a timely fashion, however events in which burst suppression would have likely been present may have been missed in this disconnection time period. Our team is currently working to develop EEG monitoring in which cords connections would be minimal to not only avoid these scenarios but also to make a safer and more efficient work enviornment for anesthesiologists to use EEG intraoperatively.

In terms of aPVT, the same system was used between pre-op and PACU values, however, use of dominant or non-dominant hand was not specificized in the protocol. Typically, in pre-op patients requested to use their dominant hand. In the PACU, patients commonly had an IV insertion in one of their two hands, and thus requested to use the hand without an IV for aPVT testing. There were occurrences in which this was the opposite hand from the one used in pre-op. A prior study on reaction time in left vs right hand mouse clicking did find that the dominant hand typical has a reaction time 180 ms faster.[55] This would account for approximately 50% of our mean change in reaction time (343.44 ms) and thus could have had a large impact on our results. In future studies it will be important to note when the hand used for aPVT testing changes.

The last limitation of this study is reflective of PACU neurocognitive measure limitations discussed earlier. With RASS being an objective measure, and thus at discretion of interviewer. The data collection by different personnel could also have led to varying degrees of scale interpretation despite the neurocognitive training given. This data set will be further analyzed to see if there were any drastic differences between researchers that could be confounding variables in this study that may need to be adjusted for.

Future Outlook

The most important take away from this study is the need for personalized anesthetic care specifically to elderly population to decrease recovery time and possibilities of long-term effects. Going forward, studies in which anesthetics can be controlled for will be important to analyze to see if specific type of anesthetics are responsible for increased recovery times, or if it is the volume and intensity of the medications. Furthermore, EEG can be introduced into the PACU, to continue analyzing brain dynamics during the actual recovery process. In the PACU burst suppression would not be present unless the patient required heavy sedation post-operation, and thus brings in our discussion of phase modulation.

As researchers spent time with patients from pre-op to the conclusion of their post-operative care, interactions with patients and healthcare providers suggested to researchers that the neurocognitive tests performed through-out the day may have actually decreased recovery time itself. From previous studies, we know that reaction time tasks have been found to increase blood flow to areas of the cortex associated with working memory.[56] Thus, the question occurs with this study- did our interactions, asking the patient to complete tasks through-out recovery or even in the pre-operative stages, actually decrease their recovery time? In practice, many clinicians have patients perform exercises in the first few days of post-operation, such as sitting-up and walking, in order to increase blood flow in the surgical areas to promote a healthy recovery from the surgical trauma. In the same sense, could mental exercises increase the efficiency of recovery for post-operative patients? Future studies comparing a neurocognitive testing intervention after surgery to a controlled post-surgical group may offer important insights to how we encourage recovery in the PACU. Another perspective on this question is the activation of brain pathways prior to induction, with neurocognitive tasks being performed pre-operatively increasing blood flow to these given areas that may prime these pathways for recovery, or simple distract the patient from surgical fears.

With this in mind, better surgical outcomes may be due to the patient constantly having hospital staff with them, listening to their pre-surgical anxieties, and easing them through conversation. Previous studies have shown a difference in pre-operative anxiety with active listening and support for patients. One study showed that this attention had a 10% increase in anxiety compared to a 47% increase in anxiety with normal patient care and attention.[57] However, this study also showed a hypnotic regimen that even decreased pre-operative anxiety in patients undergoing surgery. There is a large importance of how healthcare providers speak with anxious patients, and this may even affect the surgical outcomes. Studies focused on outcomes with different pre-operative language and post-operative tasks may open doors to better outcomes through simple changes to our surgical regimens.

Conclusions

While we have found an association between reaction time and recovery that may be utilized to optimize patient care in the PACU, there are many questions to still be answered in regard to brain dynamics and the reasons why we see these correlations. Areas of the cortex associated with reaction time and aging brains are of important relevance as we can see the strong association of reaction time to recovery. This association is also important for providing objective measures that healthcare providers and patients can rely on to ensure efficient bed utilization and length of care. Intraoperative brain dynamics, however, need further evaluation before any values can be used as predictive factors of recovery time. Further so, looking forwards towards analyzing EEG in the PACU may provide a more accurate window into the individual patient's recovery timeline. As care for the elderly and ambulatory surgeries becomes a more prominent part of our healthcare system, so should be research into finding better practices for best patient outcomes.

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