METHODS OF IDENTIFYING NEUROLOGICAL DELIRIUM STUDY

(MIND)

by

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Delirium is a major concern for critically ill older patients because it is associated with significant risk to quality of life and mortality. The United States spends approximately $164 billion in Medicare funding annually to combat the consequences of delirium. This figure is only expected to increase as the number of individuals aged 65 years or older increases. By 2030, one in four individuals in the United States will be 65 years old or older. Of further concern is that more adults are surviving critical illness and are therefore living with more comorbidities. Currently, as many as 80% of adults in intensive care units develop delirium. Unfortunately, healthcare providers fail to recognize 80% of these cases.

Delirium is an acute fluctuating disorder impacting attention and global cognitive function with an underlying organic cause. As the brain attempts to adapt to overwhelming stress, reductions in cortical activity result in neurotransmitter imbalances. These imbalances are reflected electrographically on electroencephalogram (EEG). Once the ability to compensate has been exhausted, behavioral symptoms associated with delirium begin to appear.

Standardized assessments for delirium need to be capable of early, accurate, and objective identification. EEG is the gold standard for delirium detection but is not always feasible due to cost, technical setup, and need for skilled interpretation. Currently available instruments, while effective in the clinical research setting, have not translated well into practice. As a result, they fall short of accurate detection for a variety of reasons, including intermittent and retrospective data collection and requiring examiner interpretation. The lack of objective physiological monitoring capability for delirium detection

prevents nurses and other healthcare providers from proactively managing this debilitating clinical problem. Because nurses provide frontline care to this patient population, the lack of adequate methods for detection presents a gap in nursing science. Recently developed technology, signal processed limited lead EEG, may provide an alternative to traditional monitoring methods for delirium. Limited lead EEG can provide the EEG waveform information needed to determine delirium status, is much cheaper than traditional EEG and can be applied by nurses, thereby overcoming limitations seen with traditional EEG such as cost and technical set-up. Critical care nurses currently use this type of EEG for sedation titration and monitoring. Because these monitors can analyze the most reliable biomarker, EEG, they may provide much needed objective, accurate, early identification of delirium.

The design for this study was prospective exploratory and cross-sectional. After appropriate Institutional Review Board permissions, a convenience sample of patients were recruited from the cardiac, medical and surgical intensive care units in a large southeastern academic medical center. Study data were collected by the author and prepared for analysis. Analytical methods included descriptive statistics, statistical methods to compare groups, and statistical methods to explore relationships among variables. Study results were then described and discussed.

METHODS OF IDENTIFYING NEUROLOGICAL DELIRIUM (MIND) STUDY

A Dissertation

Presented to the Faculty of the Department of College of Nursing

East Carolina University

In Partial Fulfillment of the Requirements for the Degree

Doctor of Philosophy in Nursing

by

Malissa Ann Mulkey

July 2020

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DEDICATIONS

I want to dedicate this dissertation

to my late mother and daughter, Brianna.

While you left this world prior to this part of my journey,

you provided inspiration for my dissertation

and continue to live in my heart.

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While my name is on this dissertation, it is the product of the hard work of my entire dissertation committee. Without their dedication, support and endless effort, this work would not have been possible. My sincere gratitude is expressed to my advisors, Dr. Sonya Hardin and Dr. Laura Gantt. Dr. Hardin advised me to the point of dissertation proposal defense. Without her expertise, knowledge and dedication, this study would not have been possible. Dr. Laura Gantt graciously supported me from dissertation proposal defense through completion of my PhD journey. She passionately and persistently assisted me with navigating the research environment and the many challenges that go along with being a nurse scientist.

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LIST OF SYMBOLS OR ABBREVIATIONS

ABG   Arterial blood gas

AD   Alzheimer's Disease

Ag   Silver

AgCl   Silver chloride

APACHE   Acute Physiology and Chronic Health

AUC   Area under the curve

AUD   Alcohol use disorder

BBB   Blood brain barrier

BUN   Blood urea Nitrogen

CAM   Confusion assessment method

DHHS   Department of Health and Human Services

DSM   Diagnostic and Statistical Manual

ECU   East Carolina University

EEG   Electroencephalogram

EMR   Electronic medical record

ETOH   Alcohol

F   Frontal

Fp   Frontoparietal

FTD   Frontotemporal dementia

GABA   Gamma-aminobutyric acid

GCS   Glasgow coma scale

Hz	Hertz
ICDSC	Intensive care delirium screening checklist
ICU	Intensive Care Unit
IRB	Institutional Review Board
LAR	Legally authorized representative
LSD	Lysergic acid diethylamide
MCA	Middle cerebral artery
MCC	Mild cognitive impairment
MCI	Mild cognitive impairment
MDMA	3,4-Methylenedioxymethamphetamine
MIND	Methods of Identifying Neurological Delirium
μV	Micro volts
NC	North Carolina
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NPV	Negative predictive value
NSAID	Non-steroidal anti-inflammatory
O	Occipital
PCP	Phencyclidine
PI	Primary investigator
PPV	Positive predictive value
Pz	Parietal center
RASS	Richmond Agitation Sedation Scale
REM	Rapid eye movement

RN	Registered nurse
SNF	Skilled nursing facility
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitor
SWS	Slow wave sleep
T	Temporal
TIA	Transient Ischemic Attack
TNF	Tumor necrosis factor
UMCIRB	University Medical Center IRB
UTA	Unable to assess
WASO	Wake after sleep onset
WHO	World Health Organization

CHAPTER ONE: INTRODUCTION

Delirium has long been a nursing management challenge. In the critical care environment, standardized bedside assessments are typically used to detect delirium. There is a need to improve identification and assessment through unexplored approaches. Therefore, this research sought to evaluate an alternative method to improve nurse recognition of delirium in older critically ill adults using a physiologic monitor, signal processed EEG.

This research was structured according to the East Carolina University (ECU) College of Nursing guidelines for the two-manuscript option available to doctoral students. Chapter one provides an overview of the concepts that organized the proposed research. These concepts included delirium, delirium assessments, electroencephalogram (EEG) waveform changes associated with delirium, and use of limited-lead signal processed EEG. Chapter two is a review of the literature regarding delirium, screening tools and EEG. Chapter three discusses the research methods, including descriptive statistics to identify central tendencies in participant characteristics. Inferential statistics were conducted to assess potential relationships between EEG-derived and CAM-ICU-derived delirium status. Chapter four is a manuscript describing the use of physiologic monitoring (i.e. EEG) to detect delirium. Chapter five and final chapter is a manuscript describing key research findings, including geriatric delirium demographics, and accuracy of EEG data derived from a limited-lead EEG device for delirium monitoring.

Introduction

Early detection of delirium is crucial because the longer a patient experiences delirium, the greater the risk to patient safety and overall outcome (Cole et al., 2015; Cole & McCusker, 2016). In 1983, the American Psychiatric Association (APA), in the Diagnostic and Statistical

Manual 3rd edition (DSM-III), standardized the definition of delirium as "primarily a disturbance of consciousness, attention, cognition, and perception that can also affect sleep, psychomotor activity, and emotions" (American Psychiatric Association, 1987; Eysenck et al., 1983; Spitzer et al., 1980).

Since that time, researchers have developed and evaluated more than 40 different clinical assessment tools to assist clinicians in identifying the presence of delirium (Garg et al., 2018). Posner (2007) defines delirium as "an acute confusional state impacting global cognitive function with an inability to maintain focused attention and distinguish delusions from reality (p. 369)."

Problem Statement

In 2013, the Society of Critical Care Medicine published the *Pain, Agitation, and Delirium Guidelines* (Barr et al., 2013a). These guidelines recommended routine delirium screening with a validated tool. Although numerous delirium assessment tools are utilized in hospitals, there remains tremendous subjectivity with such approaches. This subjectivity results in failure of nurses to identify as many as 80% of delirium cases (Fick et al., 2007; Inouye et al., 2001).

Background

Over the years, a variety of different names have been used for delirium. For example, in 500 BC, Hippocrates used 16 different names for delirium including *leros, mania, lethargus*, and *phrenitis* (Hippocrates et al., 1923). He claimed that acute confusion in the setting of fever was fatal. Generally, there was agreement that this "disorder of the mind" was associated with poor clinical patient outcomes.

The word *delirium* comes from the Latin word *deliro-delirare* meaning "to go out of the furrow." The term delirium appeared in medical literature as early as the first century AD. These early writings by Celcus, described mental impairment that occurred during fever and trauma to the head (Adamis et al., 2007). Celcus further expressed that while the underlying etiology may have resolved, the patient may continue to appear "insane."

Several centuries after Hippocrates, in AD 542, a historian named Procopius provided a more detailed description of delirium as a possible disease. In his writings, he described two types of delirium, hyperactive and hypoactive (Procopius, 1937). He described hyperactive behaviors as insomnia, agitation, excitement and increased physical activity. The other subset of symptoms, hypoactive delirium, included a significant increase in sleep, an inability to meet one's basic physiological needs including food and water, and not recognizing people known to the individual. Procopius went on to explain that individuals often experienced hallucinations before disease onset.

More recently, bedside clinicians have used other terms when attempting to identify delirium in particular subsets of patients such as *ICU psychosis* and *sundowning*. ICU psychosis has been used to describe the acute confusion in critically ill patients because of the high incidence of delirium symptoms. While delirium is not the only cause for night time confusion, sundowning has been used to label confusion that is more prominent among older patients at night when there is less stimulation. Geriatricians, psychiatrists, anesthetists, and intensivists prefer the term delirium, while the term "encephalopathy" has been more commonly used by neurologists (Slooter, 2017). In medicine and psychiatric literature, delirium is commonly referred to as an *acute confusional state* and *acute brain failure* (American Psychiatric Association, 1998; Martins & Fernandes, 2012).

The development of clear diagnostic criteria for delirium in the Diagnostic and Statistical Manual third edition (DSM-III) and subsequent DSM editions reflects the considerable amount of research that has been conducted in the field. The DSM-IV criteria provide a comprehensive description of delirium that has become the preferred diagnostic criteria for clinical practice and research. Subsequent studies indicate that there is considerable disparity in delirium detection between the DSM editions. For example, Meagher et al. (2014) found that concordance was 53% ($\kappa = 0.22$) between DSM-IV and strict interpretation of the DSM-5 criteria, 91% ($\kappa = 0.82$) between the DSM-IV and relaxed interpretation of DSM-5 criteria, and 60% ($\kappa = 0.29$) between the strict versus relaxed DSM-5 criteria. Criteria in the DSM-5 overlaps considerably with criteria included in the DSM-IV, but with a reduction in the capture of delirium. Although there are no major core element differences between the DSM-IV and the DSM-5 criteria, there are some differences in content and criteria wording that are thought to have an impact on the agreement of the DSM-5 with criteria from prior editions (See Table 1). Depending on how strict the criteria are interpreted, between 11% and 70% of DSM-IV determined delirium also meets the DSM-V criteria. This difference has important implications for clinical care and research (Meagher et al., 2014).

Despite a long history, the multiple names have created uncertainty regarding the etiology, with delirium remaining poorly understood and frequently defined imprecisely. As a result, when identified, delirium has often been present for several days (Heriot et al., 2017; Inouye et al., 2016). Delirium is associated with many negative outcomes, including, increased mortality rates, prolonged hospital stay, decreased physical and cognitive recovery, and higher rates of institutionalization.

Table 1. Comparing DSM classifications of delirium

Diagnostic and Statistical Manual – IV	Diagnostic and Statistical Manual – V
Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.	Disturbance in *attention* (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced *orientation to the environment*).
A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.	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.
The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day	Includes an additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).
There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.	*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.*
	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.*

Adapted from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 1998. Copyright © 1998, & American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Washington, DC, American Psychiatric Association, 2013. Copyright © 2013, American Psychiatric Association.

Note: Changes in DSM-5 from DSM-IV shown in *italics*.

Significance

Delirium affects approximately one third of all older hospitalized adults and 90% of those in the ICU environment (Oldham et al., 2017). Additionally, older adults tend to develop the more severe delirium subtype, hypoactive delirium, often called *quiet* or *lethargic* delirium. Delirium is associated with increasing hospital inpatient days by more than 17.5 million annually and further hypothesized to increase the need for long-term care (Mulkey, Hardin, Olson, et al., 2018). Because of these associated complications, the United States spends approximately $164 billion Medicare dollars a year managing complications associated with delirium (Bail et al., 2015). Patients who quickly recover from an episode of delirium have been shown to have higher levels of functional recovery than those experiencing longer episodes (Chew et al., 2017; Hshieh et al., 2017). There is a negative correlation between length of delirium and scores on Katz Index of Independence in Activities of Daily Living, a measure of a patient's functional ability when attempting to complete activities such as bathing, eating, dressing, and home maintenance (Szlejf et al., 2012). This has translated to an increased need for long-term care after hospital discharge. Along with increases in acute care costs, delirium is associated with an increase in 30-day post-discharge costs of $238,726 per patient (Elsamadicy et al., 2017). With the number of individuals older than 64 years expected to increase by greater than 50% over the next two decades, the incidence of delirium is expected to rise. Additionally, as healthcare advances and more individuals survive critical illness, healthcare systems will continue to see an increasing number of comorbidities among patients, further increasing the risk for delirium. Therefore, delirium is a national healthcare concern and warrants investigation.

Defining Delirium

The World Health Organization (WHO) standardized the definition of delirium in the 1970s (World Health Organization (WHO), 2018). However, it was not until 1983 that the American Psychiatric Association clinically standardized the diagnosis of delirium as a neuropsychiatric disorder in the *Diagnostic and Statistical Manual* (DSM), 3rd edition (American Psychiatric Association, 1987; Pichot, 1986). Today, delirium is defined as an acute fluctuating disorder of attention and global cognitive function characterized by impaired awareness and cognition, inattention, and disorganized thinking (American Psychiatric Association, 2013).

Early Identification of Delirium

Delirium is complex, may be subtle, and is highly underdiagnosed (Kluger et al., 2018). Because a physiologic monitor is lacking, nurses are hampered in providing optimal patient care and conducting research on this pervasive problem. Earlier detection, when nursing interventions would be more effective, would likely reduce the long-term ramifications (M. A. Mulkey, Everhart, D.E., Munro, C.L., Hardin, S.R., Olson, D.M., 2019). Having an objective method nurses can easily use could change the standard of care by providing earlier identification. Physiologic monitoring may also provide identification prior to symptom onset, especially in the setting of hypoactive delirium, allowing for the greatest impact on patient outcomes (M. A. Mulkey, D. E. Everhart, S. Kim, et al., 2019).

Conceptual Framework

There is a considerable body of literature describing the multiple etiologies that lead to delirium. The conceptual framework that guided this study considers these multiple pathways. Maldonado's pathoetiological model of delirium describes the evolution of delirium beginning

with a stress response (Maldonado, 2008). His model specifically looks at the neurochemical

impact of critical illness. The model goes on to describe how multiple cellular level cerebral

processes lead to the microlevel chemical changes that disrupt equilibrium. This process initiates

multiple cascades to become a vicious cycle of competition between supply and demand,

depicted as neuroelectrical changes on EEG. When the brain can no longer compensate, the

individual will begin to develop behavioral symptoms associated with delirium (See Figure 1).
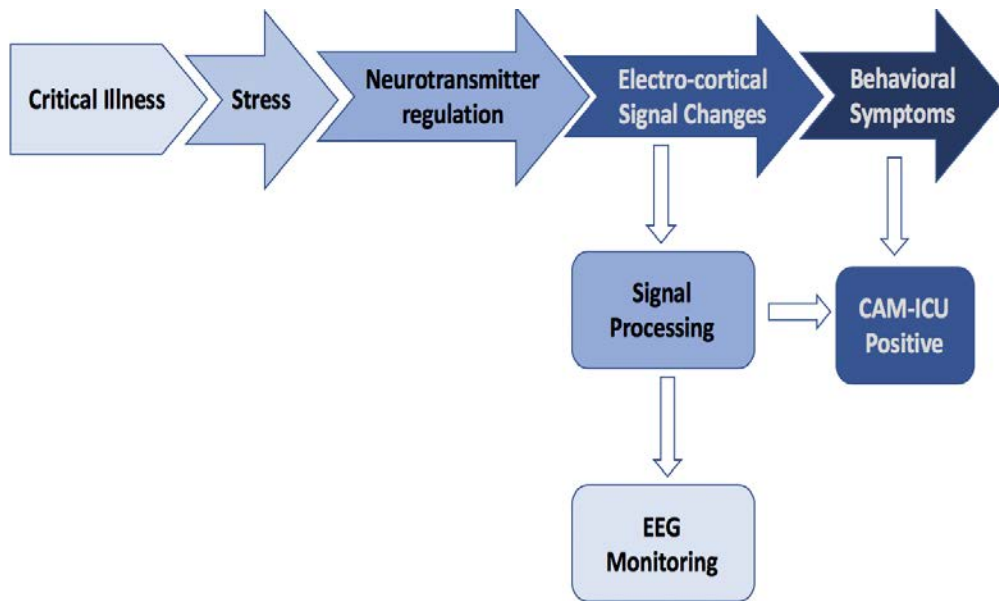
Figure 1. Pathophysiologic process and detection.

The model describes two processes: impairment of acetylcholine release and

transmission, as well as an impairment in the reuptake of and ability to convert dopamine to

norepinephrine. These impairments are further exacerbated by stress. Individual differences in

genetics then affect the physiological stress response. Having a theory driven framework

describing delirium's underlying processes guided selection of physiologic measures and patient

selection for this study. Improving nurse screening and initiation of earlier interventions in

patients at highest risk (i.e., older adults who are critically ill) will decrease the associated

morbidity and mortality. Further details regarding this model are described in Chapter 2.

<div align="center">**Definitions**</div>

Acute Physiology and Chronic Health Evaluation Score. Acute Physiology and Chronic

Health Evaluation Score (APACHE) is a method of evaluating patient severity of illness in

critically ill patients based on 12 physiologic variables, age, and underlying health ranging from

0 to 71.

Alpha. Alpha (α) is an EEG waveform frequency band of 8-13 Hertz (Hz) occurring during

wakefulness over the posterior regions of the brain, generally with maximum amplitudes over the

occipital areas (See Figure 2)
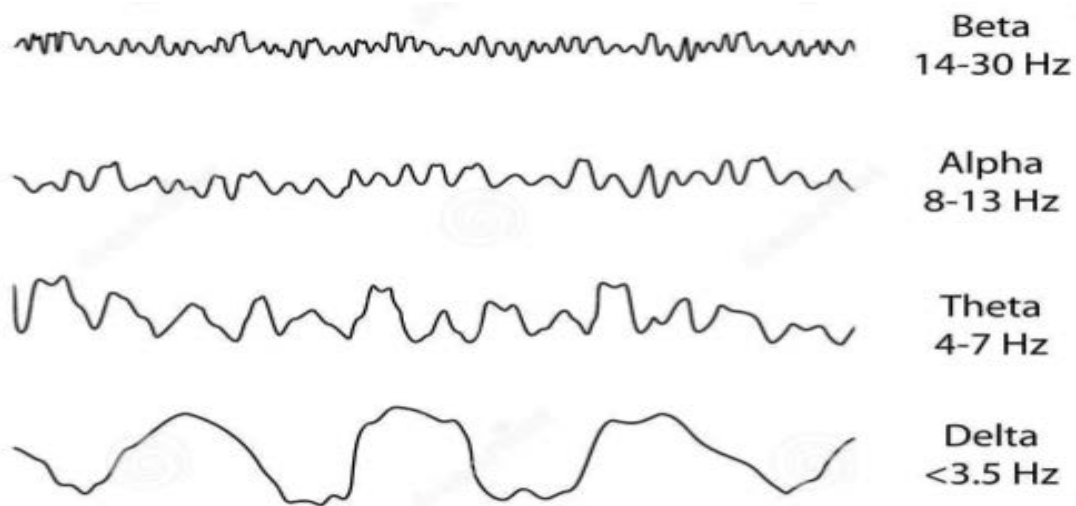
Figure 2. EEG waveforms.

Note: Reprinted from Sivakumar, S. (2017). The Wave – The characteristics of an EEG.
Retrieved from https://www.firstclassmed.com/articles/2017/eeg-waves. Reprinted with
permission.

Alpha/Delta Ratio. Alpha/Delta Ratio is the proportion of alpha waves to delta waves.

Alpha/Theta Ratio. Alpha/Theta Ratio is the proportion of alpha waves to theta waves.

Altered level of consciousness. Altered level of consciousness is a state of awareness that is

<div align="center">9</div>

anything other than alert, such as hypervigilance, lethargy, stupor or coma.

Alert. Alert is a state of being fully aware of the surroundings and interacting appropriately.

Amplitude. Amplitude is the voltage of EEG waves expressed in microvolts (µV); measured peak-to-peak (See Figure 3).

Bergen Plugins. Bergen Plugins are plugins utilized to remove artifact in MATLAB.
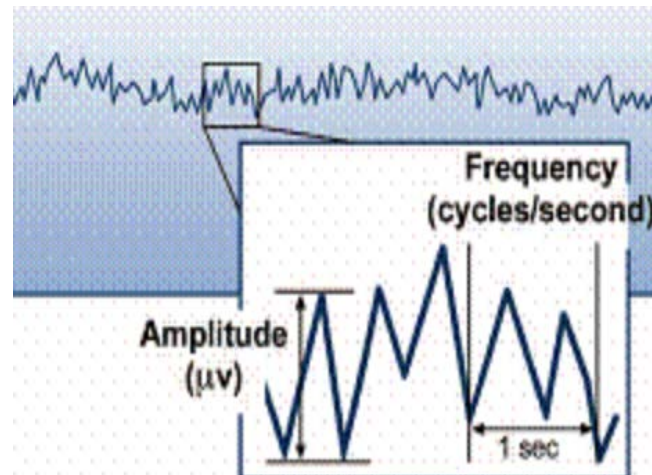
Figure 3. EEG Measurement.

Note: Reprinted from Arnesano, C. (2009). Intraoperative Detection of Awareness. Retrieved September 4, 2018 from http://bme240.eng.uci.edu/students/09s/arnesanc/bispectral_analysis.html. Reprinted with permission.

Beta. Beta (**ß)** is an EEG waveform frequency band from 14 to 40 Hz, characteristically recorded over the fronto-central regions of the head during wakefulness.

Charlson Comorbidity Index. Charlson Comorbidity Index is a scoring system that predicts the one-year mortality for a patient who may have a range of comorbid conditions, such as heart disease, Acquired Immunodeficiency Syndrome (AIDS), or cancer (a total of 22 conditions). Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one.

Coma. Coma is a state of being unarousable, unaware of the surroundings, and unable to interact with the external environment regardless of maximum stimulus.

Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). CAM-ICU is a validated delirium clinical assessment tool that is a modified version of the CAM. It is designed to allow assessment of mechanically ventilated and nonverbal adult patients with critical illness. Considered the gold standard for delirium screening (See Appendix D).

Deep sleep. Deep sleep is the 3rd and 4th stage of non-rapid eye movement (REM) sleep.

Delirium. Delirium is an acute fluctuating disorder of attention and global cognitive function characterized by impaired awareness and cognition, inattention, and disorganized thinking.

Delta. Delta is an EEG waveform frequency band under 4 Hz during light sleep or a drowsy state.

Delusion. Delusion is a false belief that contradicts rational thought or reality.

Delusional. The state of maintaining fixed false beliefs even when confronted with facts.

Derivation. Derivation is the process of recording from a pair of electrodes in an EEG channel.

Disorientation. Disorientation is a state of impaired awareness or orientation.

Epoch. Epoch is the amount of time displayed.

Frequency. Frequency is the rate per second that specifies the typical rate and range for all patterns, e.g., 1/second and 0.5-2/second.

Gamma. Gamma is an EEG waveform frequency band above 40 Hz most commonly recorded with intracranial electrodes.

Glasgow Coma Scale. Glasgow Coma Scale (GCS) is the most common scoring system used to describe the level of consciousness in response to defined stimuli (eyes, verbal, motor).

The GCS provides a score in the range 3-15; patients with scores of 3-8 are usually said to be in a coma.

Hallucination. Hallucination is seeing, hearing, smelling, or tasting something that is not there.

Hamming Windows. Hamming Windows are used to reduce EEG wave variabilities.

High frequency filter. High frequency filter is a circuit that reduces the sensitivity of the EEG channel to relatively high frequencies.

High-pass filter. High-pass filter is a low-frequency filter.

Inappropriate speech. Inappropriate speech is spoken words or utterances that lack contextual meaning.

Latency. Latency is a delay between stimulus and response or the time duration of an event.

Lethargic. Lethargic is a state of being drowsy but easy to arouse, may not be fully aware of the surroundings or spontaneously interact; becomes fully aware and appropriately interactive with minimal stimulation.

Light sleep. Light sleep is the 1st and 2nd stage of non-REM sleep.

Low-frequency filter. Low-frequency filter is a circuit that reduces the sensitivity of the EEG channel to relatively low frequencies.

Low-pass filter. Low-pass filter is high-frequency filter.

Montage. Montage is the standardized arrangement and selection of EEG channel pairs for display and review.

Precipitating factors. Precipitating factors are newly introduced (acute) conditions that trigger delirium onset including critical illness, trauma, surgery and the current physical environment.

Predisposing factors. Predisposing factors are pre-existing conditions that reduce functional reserve and adaptation to increased physiological stress including older age and pre-existing chronic conditions.

Psychomotor agitation. Psychomotor agitation is a state of restlessness with unintentional or purposeless movement.

Psychomotor retardation. Psychomotor retardation is a state of slowing of thought and movement.

REM. Rapid eye movement

REM sleep. REM sleep stage is characterized by episodic bursts of predominantly horizontal rapid eye movements. EEG activity during this sleep phase typically has a low amplitude mixed frequency, is frequently associated with dreams, phasic muscle activity, saw-tooth waves and changes in respiration may occur.

Richmond Agitation Sedation Scale. The Richmond Agitation Sedation Scale (RASS) is used to measure a patient's agitation or sedation level. It is a 10-point scale, with four levels of anxiety or agitation, one level denoting a calm and alert state, and five levels of sedation (See Appendix E).

Sleep/wake cycle disturbance. A sleep/wake cycle disturbance is an abnormality in length, timing, and/or rigidity of sleep or sleep pattern relative to the day-night cycle.

Stress. Stress is a non-specific response of the body to any demand for change.

Stupor. Stupor is a state of being difficult to arouse, somewhat unaware of some or all the surroundings or not spontaneously interactive; becomes partially aware with vigorous repeated stimulation; when the stimulus is removed, the individual returns to an unresponsive state.

Symptom fluctuation. Symptom fluctuation is a symptom that comes and goes.

Theta. Theta is a frequency band from 4 to under 8 Hz during deep sleep.

Vigilant. Vigilant is a state of hyper-alertness.

WASO. Wake after sleep onset

Purpose of the Study

This study was a trial to refine the identification of appropriate delirium biomarkers that may provide a foundation to incorporate EEG-based cognitive monitoring into acute care settings for critically ill older adults (>64 years) who are at highest risk of delirium. Therefore, the purpose of this study was to explore the ability of a commercially available limited-lead EEG monitor to detect evolving delirium.

Specific Aims and Research Questions

Aim 1: Describe EEG changes associated with delirium status based on CAM-ICU assessment in a sample of older adults admitted to the medical and surgical intensive care unit requiring mechanical ventilation.

Research Question (RQ) 1: Is there a reduction in alpha wave (awake wave) percentage with significant decreases in power, increases in theta wave percentage and power (sleep wave), and delta (deep sleep wave) and theta wave intrusion that lead to a higher theta/alpha ratio and delta/alpha ratio in patients who are CAM-ICU positive, indicating delirium?

RQ2: Is there a difference in defining EEG characteristics in those individuals admitted to the cardiac, medical and surgical ICU who developed delirium compared to those who did not develop delirium?

RQ3: Is there an inversion of the theta/alpha ratio and delta/alpha ratio?

Aim 2: Examine the relationship of the study variables and delirium status to determine representativeness of the sample.

RQ4: To evaluate the subject characteristics, do risk factors predict delirium in older (>64 years) cardiac, medical and surgical ICU patients?

Known risk factors are: age, race, gender, marital status, living situation, insurance type, drug and alcohol use, comorbidities, admission diagnosis, GCS score, APACHE mean score, ICU length of stay and hospital length of stay, and

RQ5: How does delirium impact discharge disposition and 30-day mortality?

Aim 3: Examine the data to develop a parsimonious EEG model to identify delirium in those patients admitted to the cardiac, medical and surgical ICU.

RQ5: What were the most parsimonious EEG models to predict delirium in those admitted to the cardiac, medical and surgical ICU by evaluating characteristics, trends or EEG pattern changes only present in patients who develop delirium?

Assumptions

Delirium is the result of uncompensated physiological stress from overwhelming illness, trauma or surgery. Stress is depicted chemically through imbalances in levels of neurotransmitters. Because neurotransmitters are responsible for carrying information from one cell to the next in the form of electrical activity, there are alterations in EEG pattern, speed and frequency. Distinct patterns are present and indicative of delirium. These changes can be detected using limited-lead signal processed EEG. Using an algorithm to identify these changes will provide a physiological method of delirium identification that is objective, continuous and available in a manner usable by nursing. Having the ability to detect delirium earlier will allow

for objective assessment of nursing interventions and prevention strategies in order to decrease the impact of delirium on mortality, quality of life, and long-term cognitive impairments.

Hypothesis

During delirium, there is reduction in alpha wave percentage with significant decreases in power, increases in theta wave percentage and power, and delta and theta wave intrusion that lead to a higher theta/alpha ratio and delta/alpha ratio. Therefore, the theta/alpha ratio and delta/alpha ratio are significantly higher, indicating delirium.

Impact on Practice

Nurses are the primary discipline assessing patients for delirium and are vital to prevention and intervention. Providing a method for nurses to monitor delirium status based on EEG changes would allow objective measurement and individualized treatment. Because EEG changes occur prior to behavioral changes, EEG monitoring would provide a way for nurses to identify these changes and intervene earlier in the process, thus reducing costs of healthcare and improving patient outcomes. Providing a physiologic method of identification will allow for determination and nursing interventions that are truly effective in reducing the presence and length of delirium episodes. Earlier identification and interventions will reduce mortality and long-term consequences of delirium. Increasing the reliability of delirium assessment using this type of monitoring will also provide an objective method to assess nursing interventions to determine which interventions are truly effective and individualize patient care.

CHAPTER TWO: REVIEW OF THE LITERATURE

Significance

Delirium is recognized as an indicator of increased risk for long-term cognitive impairment regardless of prior cognitive or functional challenges. Delirium affects as many as 80% of mechanically ventilated older adults in the ICU (Oldham et al., 2017). While delirium is difficult for nurses to detect, it is even more difficult in older patients due to concerns regarding possible dementia and the hypoactive delirium subtype they typically develop (Nishimura et al., 2016; Richardson et al., 2017). Because of delays in identification, most older adults still have delirium at the point of hospital discharge, posing an ongoing challenge regarding the need for facility-based post-acute care.

Brown, Ferner, et al. (2011) looking at delirium-associated cognitive impairment have focused on fluid cognitive abilities. Fluid cognition involves the active processing, controlling and sustaining of attention during tasks. In contrast, crystallized cognition depends on stored information from prior experiences, learning and overall fund of knowledge. Because the two types of cognition rely on different areas of the brain, neural events affect them differently. Crystallized cognition appears to be more constant over the lifespan, while fluid cognition steadily deteriorates over the course of time. Brown, Ferner, et al. (2011); Brown, Fordyce, et al. (2011) attempted to determine whether crystallized cognition is affected by delirium. They found that while patients demonstrate significant impairment during times of increased demand for fluid cognition, crystallized abilities are preserved. Because crystallized intelligence remains stable, it may be a reliable indicator for baseline cognitive function prior to delirium, thereby providing a means of determining the patient's baseline level of cognitive function when no one is available to provide information regarding the patient's history.

Few studies have attempted to provide a neuropsychological profile for delirium based on evaluating fluid cognitive domains. Providing an accurate neuropsychological profile of delirium requires the use of appropriate assessments to determine the impact of delirium on the cognitive domains. Therefore, using the appropriate assessments to detect alterations in cognitive function may allow clinicians to predict the onset of delirium and improve prevention.

Clinical Presentation of Delirium

During an episode of delirium, patients show impairment in several cognitive components including attention span, selective attention, and sustained attention (Posner & Boies, 1971; Stevens et al., 2014). Of the three, sustained attention – the ability to maintain focused attention on a specific stimulus – appears to be affected the most by delirium. Although inattention, delirium's core feature, is well described, the understanding of level of arousal is limited. Decreased level of consciousness can limit the ability to perform tasks that require sustained attention. This is of particular importance in the critical care environment because a change in level of arousal may indicate an increase in illness severity, delirium risk and mortality.

While attention is specified in the DSM criteria, the extent to which attention is affected by level of arousal has not been explicitly studied. Currently, it is unknown if drowsy patients generally also have impaired attention or if they frequently can have normal attention despite a reduced level of arousal. Work by Posner and colleagues (2007) and recent findings from Tieges et al. (2013) suggest the former is more likely. As a result, Tieges recommends further studies draw from this body of knowledge while also involving the development of new methods and approaches that account for these particular challenges that delirium presents.

More than 30 years ago, Posner's (1971) original model of attention suggested a close relationship between attention and arousal. His model described the decision-making process in relation to determining what stimulus to focus on in an environment with multiple competing stimuli. Posner (1971) proposed that the attention network encompasses three individual but thoroughly connected systems within the brain: alerting, orienting and executive function. The alerting network maintains optimal arousal and observes but does not act. When the alerting network transitions from general survey to focusing on something specific, the orienting network is triggered. Posner further proposed that by triggering the orienting network, all the senses are alerted and information is prioritized. This activates the executive network to decide if the selected stimuli require maintained focus. If so, processing of other available stimuli slows down.

Because attention is a core feature of delirium, most attention tests have been found to be sensitive to delirium. Considering delirium within Posner's model of attention, patients with delirium have attention deficits in all three networks, an inability or difficulty maintaining focus (alerting), prioritizing sensory input (orienting), and maintaining focus of attention when there are other stimuli competing for the individual's attention (executive control) in a stimuli intensive environment (Posner & Boies, 1971).

Attention involves cognitive processing and conscious cognitive processing over various time periods. Although attention is widely studied, no single definition exists. This is likely due to the significant overlap among the constructs of attention, working memory, and executive control. Fan et al. (2009) conducted a study to characterize possible behavioral interaction and integration in healthy adult volunteers using a revised attention network test with cue-target interval and cue validity manipulations. They found the alerting improved overall response

speed. However, it exerted a negative influence on executive control under certain conditions, supporting Posner's hypothesis of functional integration and interaction of these brain networks. Posner's model provides an explanation for this overlap. Posner proposed that lower levels of attention including sustained attention and orienting are prerequisites for higher level attentional functioning (Posner & Petersen, 1990). Posner's work provides evidence for the combination of symptoms that describe delirium and therefore also the DSM diagnosis criteria. Because arousal and attention are closely related, assessing for delirium can be challenging and therefore limit detection. There is some evidence to suggest that attention is sensitive to fluctuations over time. (Kucyi et al., 2017; Näätänen, 2018).

Research has also shown a preserved ability to sustain attention in mildly demented patients (Perry et al., 2000). Posner (1967) examined aspects of the role of memory in information processing. Posner posited that informational processing is separate from short-term memory. This suggests tests of sustained attention are able to discriminate delirium from dementia, providing support that deficits in attention differentiate delirium from dementia and other neuropsychiatric syndromes. His work also supported the concept that dementia and delirium have different neuroendocrine and therefore, neuroelectrical processes, thereby supporting the use of physiological monitoring to improve delirium detection.

Persistent Delirium

Delirium can be stressful and overwhelming for everyone involved, including the patient, family, friends and clinical staff (Bull et al., 2017). For the patient, this distress can continue after delirium has resolved (Herbst & Drenth, 2012). Inability to differentiate factual from delirious memories limits the ability to recollect memories during and surrounding delirious

episodes. Delirious memory recall may have further ramifications such as depression, anxiety, post-traumatic stress disorder and post-intensive care syndrome.

The longer delirium persists the more severe it becomes and the harder it is to alleviate (Ely, Gautam, et al., 2001; Inouye et al., 2016). Severity and length of delirium are associated with delays in liberation from mechanical ventilation, length of ICU stay, and worse overall outcomes (Zhang et al., 2017). As a result, delirium increases the risk for compromise to patient safety, lifelong health, and quality of life (Adamis et al., 2015; Wolters et al., 2017; Wolters et al., 2016). This is represented with a 10-fold increase in ongoing cognitive impairment and a three-fold increase in hospital mortality in older patients. Additionally, older adults are more prone to develop the hypoactive delirium subtype, which is less likely to interfere with treatment and, therefore, does not trigger an immediate concern among nurses. (Danila et al., 2018; Morandi et al., 2018; Wang et al., 2018).

Evidence suggests that episodes of delirium can continue for up to 6 months after hospital discharge (Gual et al., 2018; Mitchell et al., 2017). Results of longitudinal studies suggest that half of older hospitalized patients who develop delirium will continue to be delirious after discharge. One third of older adults will continue to show signs one-month post-discharge and one fourth at three months after discharge. Six months after hospital discharge, one in five older adults remain symptomatic (Mitchell et al., 2017). This suggests that most older patients will not fully recover from the delirium episode during hospitalization. Because delirium is associated with increases length of hospital stays, risk for falls, dehydration and hospital-acquired injuries that significantly increase healthcare costs, there is great need for improvement in early identification (Inouye, 2018; Shields et al., 2017).

Morbidity

Delirium is associated with poor cognitive outcomes (Jackson, Archer, et al., 2011; Jackson, Mitchell, et al., 2011). Collectively two reviews that evaluated 18 investigations including nearly 4000 patients from 1998 to 2008 documented a strong relationship between delirium and a decline in cognitive function (Jackson, Archer, et al., 2011; Jackson, Mitchell, et al., 2011; MacLullich et al., 2011). Chaudhry (2013) found that patients with cognitive impairments that persist after delirium resolves may never fully recover. Therefore, developing delirium increases the risk for ongoing decline in neuropsychological function.

While current research has primarily focused on associations between delirium and impairments in global cognitive function, emerging evidence suggests delirium has distinguishable anatomic patterns and processes. Recent studies have demonstrated that there is significant hypoperfusion in the frontal, temporal, and cortical regions of the brain. Because blood vessels supplying oxygen and nutrients to the subcortical structures are small, even slight amounts of hypoperfusion can impact key components of executive function. Even without frank ischemic injury, impairment of executive function commonly develops in these subcortical structures, including the frontal-subcortical circuitry.

Radanovich (2015) found that patients who experienced delirium were more likely to develop hospital-associated complications, have an increased need for repeat interventions, an increase length of stay have higher in-hospital mortality rates and at 30-days after discharge, compared to those who did not develop delirium. In hospital survivors, delirium was associated with an increased need for acute rehabilitation, skilled nursing and long-term acute care after discharge (Tarazona -Santabalbina, 2012). When delirium occurs in patients with prior cognitive impairment, there is also greater risk for decline in mobility, highlighting the importance of

delirium preventions and cognitive therapies (Klein et al., 2015). These interventions are thought to improve the functional recovery and reduce one-year post-discharge mortality (Mulkey et al., 2014)

Gruber-Baldini et al. (2017) conducted a prospective cohort study of 682 older patients with no pre-existing cognitive impairment at the time of admission who subsequently developed delirium. The focus of this study was to evaluate the incidence of persistent or sustained cognitive impairment based on a Mini Mental Status Exam (MMSE) and a decline in ability to perform activities of daily living (ADL) two years after hospital discharge. They found the presence of delirium resulted in fewer patients who were able to complete ADLs, walk 10 feet, and a higher incidence of depression and cognitive impairment two years after hospitalization. Edelstein et al. (2004) also found community-dwelling patients who developed delirium had an increased one-year mortality rate, functional decline, and decline in independence after hospitalization.

Mortality

There is a positive correlation between mortality rate and length of delirium episode. Researchers have found evidence to support as much as an 11% increase in mortality for each 48 hours of active delirium (Adamis et al., 2017; Avelino-Silva et al., 2018). As many as 14% of patients who experience delirium will die within 30 days and 22% at six months (Adamis et al., 2017; Avelino-Silva et al., 2018). These rates are twice the rate of comparable medical patients who do not develop delirium (Adamis et al., 2017; Avelino-Silva et al., 2018).

Conceptual Framework to Justify Use of EEG

Having a theory-driven framework to describe the underlying processes is important to assist in identification of delirium in critically ill older adults through nurse screening and

interventions. Delirium has been described as the neuroendocrine system's response to stress. It has been suggested that predisposing risk factors for delirium include age-related changes in neurotransmission, regulation of hormones, and immune response. Having multiple complex pathophysiological mechanisms involving multiple systems supports the need for identifying patients at highest risk of delirium. The pathoetiological model of delirium describes the brain's response to stress at the cellular and neuroelectrical level.

Pathology of Delirium

There are multiple theories or hypotheses attempting to describe the underlying etiologies that result in delirium. However, none of these theories completely explains how multiple etiologies end in one common pathway – delirium. For example, an inflammatory theory claims that physical stress causes an increase in proinflammatory cytokine release that alters permeability of the blood-brain barrier (BBB) but does not take into account why patients experiencing the same physical stress become delirious and others do not (Maldonado, 2017).

The pathoetiological model of delirium, developed by Dr. Jose Maldonado, describes the brain's response to stress at the cellular and neuroelectrical level by proposing there are two types of factors at play in the development of delirium (Maldonado, 2008, 2017). Predisposing risk factors increase vulnerability to delirium by reducing functional reserve. These factors include older age as well as preexisting cognitive impairment and other comorbid conditions. Precipitating factors are acute conditions that result in increased physiological stress including critical illness, trauma, surgery and the current physical environment. As stress-related processes cross the BBB and enter cerebral circulation, they initiate inflammatory immune responses that increase demands on the brain and disrupts equilibrium. These impairments are further exacerbated as the stressors increase. Individual differences in genetics then affect the

physiological stress response. These sequelae then result in "acute brain dysfunction," which is now called delirium. It is therefore likely that the syndromes of delirium are behavioral representations of one or various independent neurochemical pathways explained by a culmination of theories.

The pathoetiological model of delirium describes two processes. The first process is an imbalance in neurotransmitters such as acetylcholine and dopamine in response to overwhelming stress. The second process is impaired transmission of cortical electrical signal pathways associated with impairment in the reuptake of and ability to convert dopamine to norepinephrine. While the primary drivers are believed to be dopamine and acetylcholine, gamma-aminobutyric acid (GABA), serotonin, norepinephrine, and glutamate also play a role through their interactions with the cholinergic and dopaminergic pathways (Moretti et al., 2004; Pasin et al., 2014; Pasina et al., 2013; Qiu et al., 2016; van Munster, Bisschop, et al., 2010; van Munster, de Rooij, et al., 2010; van Munster et al., 2012). These secondary drivers appear to result in the different behavioral presentations. More specifically, the excess release of dopamine, norepinephrine, and glutamate, reduction in cholinergic function, and changes in serotonergic and GABA activity lead to distinct EEG changes and three different clinical presentations or subtypes – hypoactive, hyperactive and mixed delirium (Plaschke et al., 2007).

As a result of neuroelectrical changes associated with neurotransmitter imbalances present during episodes of delirium, although not pathognomonic, EEG waveform amplitude and latency are potentially the most reliable biomarkers of delirium (Plaschke et al., 2010; van der Kooi et al., 2012a; van der Kooi et al., 2015). By reflecting the cortex-level connectivity of the brain, EEG biomarkers can increase the sensitivity and specificity of delirium predictive models (M. A. Mulkey, D. E. Everhart, S. Kim, et al., 2019). Extracting these quantitative biomarkers

from the EEG sequence will provide better insight into delirium-related brain activity. They may also capture the dynamic nature of delirium in its earliest state, prior to symptom onset (Plaschke et al., 2010; van der Kooi et al., 2012a; van der Kooi et al., 2015). Combining these biomarkers with conventional ones will boost the predictive power of delirium diagnostic tools.

Delirium in Comparison to Other Cognitive Impairments to Justify Use of EEG

Criteria for mild cognitive impairment (MCI) and dementia are very similar, in that both involve general memory deficits that are abnormal for age. In fact, MCI is said to occur when a patient has cognitive impairments that do not meet all the diagnostic criteria for dementia (Power et al., 2017). The impairment must be greater than that explained by normal cognitive aging, normal general cognitive function, and include impairments in cognitive domains other than memory.

Unlike delirium, MCI and dementia do not have an acute onset (Inouye et al., 2016). Those with MCI maintain the ability to complete activities of daily living. For those with dementia, progressive cognitive impairments reduce the ability to carry out daily tasks. With delirium, there are impairments in the attention and level of consciousness cognitive domains. These domains are usually not impacted with dementia unless there is also concurrent or developing delirium. A relationship exists whereby patients who develop delirium are more likely to develop dementia, and dementia increases the likelihood of experiencing delirium. Although no exact number is available, estimates on the occurrence of coexistence are high (22-89%) among hospitalized older adults (Avelino-Silva et al., 2017; Ciampi et al., 2011). While these relationships remain poorly understood, explanations include the possibility that the development of delirium reflects a vulnerability to dementia and that existing neuronal damage, caused by dementia, is directly responsible for causing delirium.

Distinction between Delirium and Psychosis to Justify Use of EEG

Delirium is sometimes confused with an episode of schizophrenia, mania, or depression (considered functional psychosis). Although the prevalence of psychosis is rare, occurring in less than 3.5% of patients, it is a frequent source of diagnostic confusion. While personality changes are uncommon, they can occur in cases of persistent delirium. When patients experience major stressors, the psychological stress can present as a form of psychosis. During a psychotic episode, patients may exhibit hallucinations, catatonia, incoherent thoughts, and emotional distress. Like delirium, the onset can be acute; however, the patient has likely had previous psychotic episodes (Johnson, 2001).

Johnson (2001) described some clinical differences that may be helpful in distinguishing between delirium and psychotic episodes such as those seen with schizophrenia. He claimed that psychotic patients are more likely to have intact short-term memory and remain oriented to time and place. Unlike delirium, schizophrenia is known to cause patients to claim to be a person in high authority such as Jesus or a well-known president such as George Washington. While hallucinations can occur in both schizophrenia and delirium, they tend to be more auditory in the setting of schizophrenia (Johnson, 2001). Delirious hallucinations tend to be more visual or both visual and auditory.

During a manic episode, patients may be described as easily distractible, insomniac and agitated. They may also be confused and experience delusions, hallucinations, and catatonic symptoms. Hallucinations may even be visual, like those typically seen in delirium. However, while the patient may be disorientated, there is typically no etiological factor and EEGs are typically normal (Johnson, 2001).

Conversely, because hypoactive delirium can mimic depression, these patients are often considered to be depressed. The patient may also have a history of depression. Both delirium and depression can coexist with dementia, further increasing complexity (M. A. Mulkey, Hardin, S.R., Olson, D.M., Munro, C.L., Everhart, D.E., 2019). A depressed or low mood is typically exhibited prior to the onset of delirium-related cognitive deficits. The patient is typically oriented, even though unreliable answers may be given. Unlike delirium, there are typically no fluctuations of attention and the patient maintains the ability to provide a reliable history of their current illness without being distracted.

Dubin et al. (1983) described four screening criteria they claimed reliably distinguished patients with organic disorders from those with functional disorders, including abnormal vital signs, disorientation, an altered level of alertness, and clouded consciousness. Although their sample of delirious patients was quite heterogeneous (typically >40 years of age with no prior psychiatric history) they claimed EEG may be helpful when attempting to differentiate between organic and functional disorders. EEG usually shows slowing of the background rhythms in delirium (Charlton & Kavanau, 2002). However, because serial EEGs are needed to exclude delirium, they felt further study was needed to determine the frequency of EEG abnormalities in patients with psychotic symptoms. Since that time, EEG technology has advanced significantly.

Psychosis and EEG

Gamma frequencies are associated with several cognitive functions, including sensory integration, attention, and memory (Snyder et al., 2015; Thibodeau et al., 2006). There is a strong relationship between beta-gamma band frequencies (>12 Hz) and cognitive processes. A coexistence of gamma frequencies and cognitive decline in patients with neuropsychiatric disorders has been observed. Elevated gamma activity has also been linked to social problems

(Arikan et al., 2018). Therefore, investigators believe resting gamma activity may be a biomarker for neurocognitive problems such as poor insight (Arikan et al., 2018).

Studies have shown Alzheimer's patients have a loss of gamma oscillations as compared to healthy controls. While patients with schizophrenia typically have low evoked gamma activity, there tends to be increased resting gamma activity in the left parieto-temporal lobe compared to controls (Arikan et al., 2018). Decreased beta activity, reduced phase synchrony in beta bands, and higher beta-gamma power occur when there are impairments in perception and working memory, such as with schizophrenia (Arikan et al., 2018). While the relationship between beta-gamma power and insight has been studied, their relationship with illness severity needs further investigation.

Memory loss does not just affect older people. Relationships between delirium and other types of dementia also hold true. Onset of one type, for example, frontotemporal dementia (FTD), tends to occur between the ages of 45 and 60 years (Young et al., 2018). Frontotemporal dementia is a group of related conditions that are the result of progressive degeneration of the temporal and frontal lobes of the brain. Frontotemporal dementias are often misdiagnosed as depression, schizophrenia or Alzheimer's disease (M. A. Mulkey, 2019; M. A. Mulkey, D. E. Everhart, & S. R. Hardin, 2019) As the condition's progressive degeneration evolves, there is gradual decline in decision-making ability, behavioral control, emotions and language.

Because there is no clear picture in the literature, the clinical distinction between FTD and Alzheimer's (AD) may be difficult (M. A. Mulkey, Everhart, D.E., Hardin, S.R., Olson, D.M., Munro, C.L., 2019). As a result of using different patient groups, equipment, parameters and metric properties, some differences, although inconsistently represented, have been seen in patients with FTD. EEG studies have revealed that patients in the early stages of FTD and AD

display different patterns in the cortical localization of oscillatory activity across different frequency bands and in functional connectivity (Nardone et al., 2018).

One subtype (behavioral variant FTD) has been found to exhibit increases in the phase lag index in the delta band, regional connectivity differences, and frontal alterations in the alpha band with no differences in beta bands (Dottori et al., 2017). Other research has shown reductions in beta bands during active tasks and an increase in the alpha band without a report of further evaluation. Similarly, not all studies have shown differences in connectivity when comparing patients with FTD patients to controls.

Factors Associated with Neurotransmitter Imbalances to Justify Use of EEG

Risk factors for neurotransmitter imbalances can be divided into two categories: predisposing and precipitating factors. Predisposing risk factors include: advanced age, co-morbid conditions, preexisting cognitive impairment, depression, and a history of drug or alcohol abuse (Adogwa et al., 2018; Bohlken & Kostev, 2018; Tully et al., 2010). Precipitating factors include acute illness, trauma, and injury (Bohlken & Kostev, 2018). While not a direct risk factor, functional impairment is particularly related to activities of daily living, increases the risk for fall-related injury and infections that can precipitate delirium (Adamis et al., 2011). The precipitating factors found to be most strongly associated with delirium are hypoxia, anoxia, metabolic abnormalities, introduction or withdrawal of psychoactive or anticholinergic medications, infection, sleep deprivation, and use of urinary catheters (Mulkey, Hardin, Olson, et al., 2018). Illness severity and presence of comorbid conditions that increase acuity, often described using the APACHE II scale, are significantly higher in patients who develop delirium and are therefore also thought to be precipitating risk factors (See Table 2).

Table 2. Neurotransmitter's role and impact related to delirium

Neurotransmitter	Role	Cause for increase	Cause for decrease	Impact
Dopamine	Reward-motivated behavior, cognition, movement Precursor to norepinephrine	Hypoxia, hypoxemia		Dramatic rise increases psychomotor activity such as distractibility, combativeness, hyper-alertness, irritability, restlessness, and delusions/hallucinations
Acetylcholine	Muscle contraction, pain response activation, regulated endocrine system, REM sleep		Older age, poor oxygenation, prior cognitive impairment, sedative, opioids	Alteration in arousal and cognition, attention, memory, REM sleep, disorientation
Norepinephrine	Catecholamine acting on α and ß receptors, fight/flight response Converted to epinephrine	Stress response activation (i.e., trauma, sepsis, cardiopulmonary arrest), vasoactive medications, thyroid hormone imbalance, anesthesia	Alcohol use/abuse, hypoxemia hypoxia hypoglycemia	Burst firing-fight or flight Tonic low-grade firing-sleep, concentration, stress resilience, inflammation
Serotonin	Regulates mood and social behavior, appetite and digestion, sleep, memory, sexual desire and function		Alcohol withdrawal, older age, abrupt withdrawal of psychiatric meds, Parkinson's disease	Acute change in mental status or behavior, increased muscle tone, clonus, hyperreflexia, hyperthermia
GABA	Regulating communication between brain cells, inhibits neuronal activity	Alcohol, sedatives, hypnotics, infection, electrolyte imbalance, some antibiotics	alcohol, sedatives, hypnotics, stress infection, electrolyte imbalance, some antibiotics	Reduces neuronal excitability to reduce stress response and over excitability, regulates muscle tone

Glutamate	Learning and memory Activated by microglial cells	Alcohol, sedatives, hypnotics, hypoxia, infection, electrolyte imbalances	Alcohol, sedatives, hypnotics, hypoxia, infection, electrolyte imbalances	Apoptosis, reduces neuroprotection, alters cerebral blood flow, may lead to electrolyte imbalances, transport of other neurotransmitters, prevention of REM sleep, immune response, cerebral metabolism
Glucocorticoids/ Cortisol	Blood sugar levels, regulate metabolism, help reduce inflammation, assist with memory formation, salt and water balance, and blood pressure	Infection, trauma, older age, steroids, anesthesia		Regulate metabolism, coping in response to stress. Can lead to catecholamine disturbances, memory disturbances, errors in information processing, confabulation, neuron viability

(Albert et al., 2014; Bilotta et al., 2013; Cochen et al., 2005; He et al., 2014; Inouye, Marcantonio, et al., 2014; Maldonado, 2008; Maldonado, 2013; Phua et al., 2011; Shields et al., 2017; Sinvani et al., 2018; Tully et al., 2010; van der Kooi, 2014, 2015; van Munster, Bisschop, et al., 2010; van Munster, de Rooij, et al., 2010; van Munster et al., 2012; van Munster et al., 2011; Wang et al., 2016; Zhang et al., 2018)

Aging to Justify Use of EEG

Aging (particularly >70 years) is one of several independent predictors, tripling the risk for delirium (Albert et al., 2014). Studies investigating the influence of age on acetylcholine release from the hypothalamus have demonstrated that, during a stress response, older age independently predicted a reduction in certain types of acetylcholine (See Table 1) throughout the brain (Maldonado, 2008, 2017). The ''neuronal aging hypothesis'' is closely related to the neurotransmitter changes observed in normal aging. The theory proposes age-related reductions in cerebral oxidative metabolism and a decrease in the number of acetylcholine producing cells increase vulnerability to even mild stress related changes, such as infection. This reduction is associated with changes in cerebral stress-regulating neurotransmitters and cellular signaling

systems that significantly increase delirium risk. Therefore, even a mild stress response is associated with a decrease in cognitive function.

As one ages, there is also a decline in cardiovascular and respiratory functional reserve. For example, by age 85 there is a 40% reduction in vital capacity, such as a decrease in baroreflex response to changes in blood pressure. These changes can magnify the effects of any coexisting cardiovascular disease (Maldonado, 2017). As a result, a reduction in the ability to compensate during times of metabolic stress can decrease cerebral oxygen delivery.

Preexisting Cognitive Impairment to Justify Use of EEG

There is a strong correlation between neurodegenerative disease and cognitive decline due to brain disconnectivity and loss of reserve. Prior cognitive impairment, such as dementia, is a significant independent risk factor for delirium (Bayindir et al., 2000; Gani et al., 2013). In the case of dementia, such as Alzheimer's disease, there is a progressive neuronal pathology likely beginning as much as twenty years before clinical diagnosis. Over time there is progressive loss of synaptic terminals and accumulation of white matter pathology. Behavioral symptoms represent brain disconnectivity and quantifiable loss of cerebral "reserve." This loss of cerebral reserve increases the risk for delirium with the advent of physiological stress.

Disruption of the Blood-Brain Barrier to Justify Use of EEG

Under normal conditions, the BBB restricts cytokines, toxins, and a multitude of medications present in the blood stream from traveling across capillaries into the brain. Therefore, the brain is relatively safeguarded from the deleterious effects of systemic inflammation. The ''physiologic stress hypothesis'' suggests that stressful situations, such as trauma, severe illness, and surgery, result in alterations in norepinephrine, thereby increasing BBB permeability (Bilotta et al., 2013). Similarly, the ''inflammatory hypothesis'' suggests that

physical stress increases the secretion of proinflammatory cerebral cytokines, thereby altering neurotransmitter activity. These proinflammatory cytokines, including interleukin and tumor necrosis factor (TNF), induce behavioral, endocrine and autonomic features of sickness behavior, an energy-conserving adaptive response to combat acute inflammation (Maldonado, 2017; van der Kooi et al., 2015).

Significantly higher levels of cytokines have been found in older patients who developed delirium within 48 hours of hospital admission compared to those without delirium. Because the BBB is impaired, chemokines (locally acting cytokines), augment the migration of inflammatory cells into the cerebral tissue. Subsequently, the brain becomes more susceptible to the effects of systemic inflammation. For example, tissue damage, adrenal stress response, cardiopulmonary bypass, and anesthesia result in transient increases in inflammation 10 to 100 times higher than normal. As stress increases, alterations in neurotransmitter synthesis and cerebral chemokine release lead to the evolution of delirium frequently called "encephalopathy" (Maldonado, 2008, 2017).

The "cellular-signaling hypothesis" suggests there is a fundamental process, like disturbances in intraneuronal signaling, that affect neurotransmitter synthesis and release (Maldonado, 2008, 2017; Maldonado, 2013). Endothelial function is a major determinant of microvascular blood flow and a key component of the BBB essential to brain function during critical illness. Therefore, endothelial dysfunction may lead to delirium by way of reducing cerebral blood flow, releasing biochemical mediators, and increasing BBB permeability (van der Kooi et al., 2012a). Studies suggest that baseline organic cerebral disorders (e.g., cerebrovascular disease) are associated with an increased risk of cerebral tissue damage in the presence of hypocapnia. Because anesthesia-related hypocapnia increases the risk of cerebral tissue damage,

it may be responsible for the enduring postoperative delirium, especially in patients with preexisting cognitive impairment or brain injury.

A multitude of factors impact the patient's hypoxic response including environmental conditions, comorbidities, and pattern and duration of the hypoxic insult. Extrinsic factors such as pump failure lead to hypoperfusion, hypoxemia, hypoxia, and reduced cerebral blood flow (Maldonado, 2008, 2017; Maldonado, 2013). Ongoing cellular injury further contributes to the neurobehavioral features of delirium, primarily signs of the hyperactive subtype, including increased psychomotor activity, hyper-alertness, agitation, irritability, restlessness, combativeness, distractibility, delusions, and hallucinations.

The ''oxygen deprivation hypothesis'' proposes that hypoxia is related to a decrease in cerebral oxidative metabolism that causes widespread reconfiguration of neuronal networks. Inadequate oxidative metabolism results in an inability to maintain ion gradients (potassium, sodium, and calcium channels) causing alterations in neurotransmitter production, metabolism, and release, and a failure to effectively eliminate neurotoxins. Rapid depletion of energy stores results in excitotoxic cell death, cerebral ischemia and neurotransmitter dysfunction. Hypoxia, hypoglycemia, and hypoperfusion result in decreased acetylcholine production and a significant release of dopamine and glutamate (van der Kooi et al., 2015). Oxygen-dependent conversion of dopamine to norepinephrine is significantly decreased (See Table 1). This reduction inhibits enzymes required for dopamine and toxic metabolite degradation, leading to even more amassment of dopamine.

A study of ICU patients investigated whether oxidative metabolic stress was present within the 48 hours prior to development of delirium. Researchers found patients with delirium had significantly lower hemoglobin, hematocrit, and oxygen saturation (measured using pulse

oximetry) values (Seaman et al., 2006). Similarly, delirious patients were more likely to show signs of increased oxidative stress (e.g., sepsis, pneumonia). For example, oxygen supply and demand imbalances in patients with sepsis, lower hemoglobin level, impaired cerebral blood flow, and decreases in cerebral oxygen delivery occurred with severity based on the underlying cause. In addition to hypoxia, critically ill patients are more likely to experience secondary mild ischemic injury, further galvanizing oxidative failure. Because of the correlation between these events and the clinical signs and symptoms of worsening deliria, there is a strong argument for the theory that neurotransmitter imbalances are the result of oxidative failure, thereby increasing delirium risk, particularly of the hyperactive and mixed delirium subtypes.

Dehydration/Electrolyte Disturbances to Justify Use of EEG

Abnormal laboratory measurements reflect the presence of an underlying pathology. As a result, altered chemistry, complete blood count, renal and liver function are indirectly associated with increasing delirium risk between 40% and 500% (Inouye, Westendorp, et al., 2014). Abnormal glucose and electrolyte levels (i.e. sodium and potassium) can lead to changes in mental status and other signs of delirium. Hyperglycemia, hypoglycemia and anemia increase delirium risk due to their effects on cerebral metabolism and oxygen transport (Albert et al., 2014). Serum albumin is responsible for oncotic pressure and elicits drug and hormone binding activity along with antioxidant and oxygen radical trapping that prevents toxic cognitive impairment. Therefore, the concentration of serum albumin can also impair cognitive performance and is a risk factor for delirium.

Impaired renal function (blood urea nitrogen [BUN]/creatinine with a resulting ratio > 18) is an indirect predisposing delirium risk factor (Davis et al., 2015). Increased BUN/creatinine levels may indicate dehydration, congestive heart failure, or other conditions that contribute to

the evolution of delirium. Electrolyte abnormalities, especially hyponatremia (sodium <130 mEq/dL) frequently seen in older patients, may be the result of renal disease or chronic diuretic therapy (Albert et al., 2014). Low serum sodium levels can lead to cellular swelling, causing anoxic depolarization. Dehydration and fluid deficits also contribute to delirium through low cerebral and renal perfusion, an increase in concentration or decreased ability of the kidneys to eliminate drugs, metabolites and toxins. Research has also discovered neuronal mitochondrial damage and glutamate hyper-transmission in the setting of dehydration (Guo et al., 2017).

Postoperative hypoactive delirium occurs more frequently in older patients with preoperative anemia or high perioperative blood transfusion volumes (Davis et al., 2015; Peterson et al., 2006). Older age and anemia may both be signs of chronic disease burden and result in a reduction in the ability to respond to stressors. Although not the only explanation, both are thought to be an indicator of frailty. Frailty is a state of diminished physiological reserve that increases the risk for disability and limits functional reserve.

Sleep Deprivation/Disruption in Circadian Rhythm to Justify Use of EEG

Sleep is a physiologic state needed to restore physical and mental functions. Sleep deprivation (36-consecutive hours or more) can cause symptoms of emotional distress (i.e., becoming easily agitated, exaggerated emotional responses, and mood swings). ''Chronic partial sleep deprivation'' (i.e., repeatedly sleeping ≤ 4 hours a night) leads to an increased impairment in attention, reduced ability to critically think, delayed response, and short-term memory loss. Delirium and sleep deprivation share many features. Both: (1) affect most ICU patients, (2) have common hallmarks (e.g., inattention, cognitive dysfunction, and fluctuations in mental status) and similar risk factors (e.g., benzodiazepine and opiate use), (3) affect the same regions of the brain, and (4) involve acetylcholine decreases or dopamine increases.

On average, ICU patients get less than two hours of sleep each day with as many as 61%

reporting sleep deprivation, making it one of the most frequent stressors (Locihova et al., 2018).

Sleep deprivation in the ICU is associated with the need for frequent treatments, interventions

and diagnostic procedures, pain, fear, high noise levels, light exposure, medication, need for

mechanical ventilation, and the primary illness (Boesen et al., 2016). Moreover, WASO is likely

secondary to noise (alarms) and light stimulation that are ever present in the ICU. Sleep

deprivation and disruption are associated with changes in mental status and memory deficits in

patients with critical illness. In most ICU settings, nurses perform serial assessments every one to

two hours, which inhibits the ability for sleep durations >2 hours. Poor sleep quality, particularly

in the ICU setting, is associated with development of delirium as well as the subsequent failure

of noninvasive ventilation in patients with acute respiratory failure (Dessap et al., 2015).

Light exposure and other environmental factors play a significant role in maintaining the

circadian rhythm. The amount of light exposure affects nighttime secretion of melatonin, a

neurohormone derived from serotonin (Burry et al., 2017). ICU patients have limited exposure to

natural and phasic light (Bilotta et al., 2013). Studies of older hospitalized patients have

demonstrated hyperactive delirium is associated with lower levels of melatonin while the

hypoactive subtype is associated with higher levels. Additionally, sepsis, systemic inflammatory

response, hormone interactions, medications, critical illness, burns, and mechanical ventilation

can also alter the excretion of melatonin.

Studies regarding melatonin levels have revealed a cessation of melatonin release in

deeply sedated ICU patients. Sedatives (benzodiazepines and propofol) and opioids inhibit REM

sleep and SWS. Because of promoting lighter sleep stages, there is a reduction in restorative

sleep. The insufficient melatonin leads to reductions in GABA that are associated with fragmented sleep/wake cycles, disruption in circadian rhythms, and nighttime awakenings.

Immune system cytokine synthesis is thought to regulate normal sleep by decreasing REM and increasing non-REM sleep. The immune system is also sensitive to sleep deprivation. Acute and chronic sleep deprivation have been associated with a reduction in the number of white blood cells, including natural killer T cells, reduced interleukin production, and reduced effectiveness of immunization, thereby creating a vicious cycle. These effects can be intensified when there is an inflammatory event.

Medications and Polypharmacy to Justify Use of EEG

The number of medications and the medications' anticholinergic potential and psychoactive properties can increase delirium risk (Mulkey, Hardin, Olson, et al., 2018). Polypharmacy (defined as more than three medications) significantly increases delirium risk as much as four-and-a-half-times. The number of medications is likely related to changes in pharmacokinetic or pharmacodynamics effects (e.g., drug-drug interactions, inhibiting drug metabolism, and synergistic negative effects).

Exposure to anticholinergic agents has been shown to independently increase the risk for developing delirium and the subsequent increase in severity of symptoms. In older patients, medications with greater anticholinergic properties increase delirium risk as much as 2.38 times with acute illness, even after adjusting for admitting diagnosis, elevations in white blood cell counts, and physical impairment (He et al., 2014). Similarly, impaired physical performance and functional status have been associated with use of anticholinergic medications in older adults (i.e., >80 years) and, therefore, an increased risk for delirium.

Psychoactive drugs also pose significant risks for delirium. Sudden withdrawal of serotonin reuptake inhibitors (SSRIs) is associated with psychologic and neuropsychiatric syndromes, including delirium. Several studies have shown medications with psychoactive activity (i.e., opiates, benzodiazepines, corticosteroids, and nonsteroidal anti-inflammatory agents [NSAIDs]) are a major contributor in up to 75% of delirium cases.

Sedatives contribute to delirium by: (1) interrupting sleep/wake cycles (i.e. increased cortical activity and significant reductions in REM and SWS; (2) eliciting a centrally mediated deficiency in acetylcholine; (3) enhancing neuronal damage by NMDA; (4) interfering with melatonin release and, therefore, the circadian rhythm; and (5) BBB disruption resulting in hyper-arousal and sensory overload (Mulkey & Everhart, 2020). Although the various sedatives may exert activity differently, all of them increase delirium risk. Approximately 90% of patients requiring mechanical ventilation receive opioids and/or benzodiazepines with approximately 80% of those developing delirium (Ghaeli et al., 2018; Singh et al., 2017; Steinseth et al., 2018). Lorazepam has been found to increase the risk for daily transition to delirium. While not the only reason, reduced levels of GABA from withdrawal of hypnotics or sedatives also increases delirium risk (See Table 1). Although not a GABAergic, studies have found dexmedetomidine activates α2-adrenergic receptors in the central nervous system and inhibits norepinephrine release, thereby reducing concentrations by 90%. This activity produces sedation, anxiolysis, and analgesia through net pathways (Mulkey & Everhart, 2020; Rowe et al., 2015). Higher incidence of delirium has been found with atropine, ketamine and propofol when compared to some of the anesthetics (Albert et al., 2014).

Opioid Use to Justify Use of EEG

Pain is an important precipitating factor for delirium (Swart et al., 2017). Unfortunately, opioids frequently used for pain control, can also lead to delirium with over and under-treatment (Swart et al., 2017). Delirium risk differs because of pharmacokinetic and pharmacodynamic properties. Opioids, in general, are known to inhibit SWS (non-REM stages 1 & 2) and REM sleep (restorative sleep) (Swart et al., 2017). Additionally, neuropathic pain can activate microglia cells and lead to an inflammatory state (Barr et al., 2013b). The mechanism of action is believed to result from an increase in dopamine and glutamate activity along with a decrease in acetylcholine activity, thereby increasing delirium risk.

Alcohol Use to Justify Use of EEG

Studies have shown that a history of alcohol or illicit drug use (i.e., cocaine, heroin, and marijuana) increases delirium duration and risk 2.4 times. Alcohol use disorder (AUD) is defined as a chronic relapsing brain disease characterized by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using (National Institute of Health Alcohol Use and Alcholism [NIAAA], 2018). Fifty percent of adults meet these criteria. Of those, half will experience withdrawal symptoms if they stop drinking, and 5% will develop delirium tremens. Alcohol withdrawal increases metabolism and norepinephrine release, while reducing α2-adrenoceptor function and serotonin levels, and altering the neuroendocrine responsiveness to norepinephrine and serotonin (Wang et al., 2014).

Wernicke's encephalopathy is a type of delirium linked to AUD and malnutrition. Alcohol use disorder is associated with a vitamin B6 deficiency, which limits the release of GABA, also increasing the risk for delirium (Brotherton et al., 2016). Delirium associated with

liver failure has also been associated with increased cerebral serotonin and impaired glutamate function.

Illicit Drug Use to Justify Use of EEG

Patients who experience hyperactive delirium are typically younger and the delirium is frequently pharmacologically induced (Davis et al., 2015; Peterson et al., 2006). About 35% of substance users will exhibit signs of agitation (Carlson et al., 2012). Robinson et al. (2011) found that substance withdrawal among trauma ICU patients was common, with 15% of the delirium being the hyperactive subtype.

Signs and symptoms from the various illicit/recreational drugs vary. For example, cocaine withdrawal is characterized by increased appetite, agitation, depressed mood, psychomotor retardation, fatigue, sleep disturbance, and vivid dreams (Blackmore et al., 2014). Toxicity from synthetic cannabinoids includes tachycardia, hypertension, nausea, confusion, dizziness, chest pain, agitation, drowsiness, hallucinations, and delusions (Blackmore et al., 2014). New designer drugs, such as synthetic cathinones (i.e., bath salts) and NBOMe compounds, a derivative of phenethylamine that increases potency, are primarily ingested for the euphoric effects including methamphetamine, lysergic acid diethylamide (LSD) and phencyclidine (PCP) are also associated with delirium (Byard, 2017). A serotonin depletion can occur if a chronic MDMA (ecstasy) user suddenly stops, creating a withdrawal syndrome (Blackmore et al., 2014). While any drug can independently illicit a serotonin syndrome, if multiple drugs associated with serotonin syndrome are taken together, the risk is higher. For example, cocaine, amphetamines, and opioids (Blackmore et al., 2014).

Detection

There have been almost 800 articles written over the past 30 years attempting to validate a variety of delirium screening tools. While there are several systematic reviews describing ICU delirium screening tools, to date, there is no single review of available geriatric screening tools (Mulkey, Roberson, et al., 2018). Current national guidelines for psychiatry, geriatrics, and critical care strongly recommend routine screening for delirium. However, due to lack of enough evidence, neither the American Psychiatric Association nor the American Geriatric Society recommend a particular tool for delirium screening. Despite these multiple attempts to develop a screening tool capable of accurately identifying delirium, more than 80% of delirium continues to go unrecognized (Heriot et al., 2017; Inouye, Westendorp, et al., 2014).

Based on current evidence, the Society of Critical Care Medicine's *Pain, Agitation, and Delirium* guidelines recommend two critical care screening tools: The CAM-ICU and the ICDSC (Barr et al., 2013b). Both tools are bedside clinical assessments to detect the behavioral symptoms resulting from delirium and have been well-validated in research settings (Ely et al., 2007; Pun & Dunn, 2007). The CAM-ICU and ICDSC have been determined to be the most valid, reliable, and feasible delirium assessment tools for use in adult ICU patients. Of these two tools, only the CAM-ICU is considered validated in both geriatric and ICU patients. The CAM-ICU is the most studied and as a result, has been described in the literature as the gold standard for assessing delirium in the ICU setting.

Physiological Measures

In 1924, human EEG waveforms were discovered using a two-channel, six-electrode system (Zeidman et al., 2014). While assessing EEG changes, it became apparent that alterations in awareness resulted in EEG changes that progressed the longer the alterations persisted

(Zeidman et al., 2014). Since then, a connection between delirium and EEG has been well established in the literature (Evans et al., 2017; Fleischmann et al., 2018; Jacobson et al., 1993; Koponen et al., 1989; Plaschke et al., 2010; Plaschke et al., 2007; van der Kooi et al., 2012a; van der Kooi, Slooter, et al., 2014; van der Kooi et al., 2015).

The EEG measures electrical impulses by employing multiple metal electrodes that are applied to the surface of the scalp in a specific arrangement (See Figure 2) requiring trained technicians for setup. The range of EEG signals in a typical adult is about 10 to 100 µV in amplitude when measured from the scalp. The level of neurotransmitters available for carrying information in the form of electrical impulses from one cell to the next dictate the speed, frequency and pattern of the electrical activity (Slooter et al., 2017). Analysis includes (1) frequency, (2) amplitude, (3) regularity and degree of organization, (4) paroxysmal features, (5) focal abnormalities and (6) wave form characteristics (See Figure 3).

Although the EEG is typically used to diagnose epilepsy, other uses include assessing the depth of anesthesia and diagnosing sleep disorders, coma, encephalopathies, and brain death (M. A. Mulkey, D. E. Everhart, S. Kim, et al., 2019). As a physiological measure, it is also capable of identifying delirium (Jacobson et al., 1993; Plaschke et al., 2010; Plaschke et al., 2007; Trzepacz et al., 1992; van der Kooi et al., 2012a; van der Kooi, Rots, et al., 2014; van der Kooi, Slooter, et al., 2014; van der Kooi et al., 2015). For example, given prior studies detected differences with dementia, Koponen et al. (1989) conducted one of the earlier studies to explore the possibility of EEG detecting delirium. Because various states have different speeds and frequencies, they are detected on EEG. Delta and theta EEG signals are usually observed in people only when they are drowsy or asleep while alpha and beta signals are observed when people are active. Alpha waves have a high frequency (range) while sleep/deep sleep

frequencies ranges are lower. The high-frequency gamma signals are observed only in cases of cross-modal sensory processing.

As delirium evolves and levels of neurotransmitters change, there is an increase in a drowsiness state and reduction in awareness that ends in sleep pattern disturbances. These changes can be monitored using EEG (van der Kooi, 2014; van der Kooi et al., 2015). In the case of delirium, this is depicted electrically as generalized slowing of background activity, slowing of awake waves (alpha waves) with significant decreases in power, increases in sleep wave (theta wave) and deep sleep wave (delta wave) power and intrusion of sleep/deep sleep waves into awake wave patterns (Plaschke et al., 2007; van der Kooi, 2014). Therefore, the ratio of sleep waves to awake waves (theta to alpha and delta to alpha) are significantly higher in the presence of delirium. As severity of delirium increases, interruptions in sleep-wake cycles increase and are depicted in further alterations in EEG waveforms (van der Kooi et al., 2012a; van der Kooi et al., 2015). These unique changes in EEG waveform characteristics are diffuse, throughout the brain, and consistent across patients with delirium regardless of underlying pathology (Haas, 2003; Zeidman et al., 2014). Therefore, the sequence of events includes increasing stress, neurotransmitter imbalance, and EEG changes, followed by behavioral signs and symptoms (Numan et al., 2017) (See Figure 1).

EEG waveform amplitude and latency are currently the most reliable biomarkers of delirium. Studies have shown traditional full quantitative EEG alone is able to differentiate delirium from non-delirium with 100% sensitivity and 96% specificity, and from dementia with 83% accuracy (Thomas et al., 2008; van der Kooi et al., 2015) (See Figure 4). As such, EEG monitoring is the gold standard for detecting the evolution of delirium (Dosa et al., 2007; McNicoll et al., 2005). However, long-term EEG monitoring is not practical because it is

expensive and re extensive technical setup and skilled interpretation that are frequently not available.
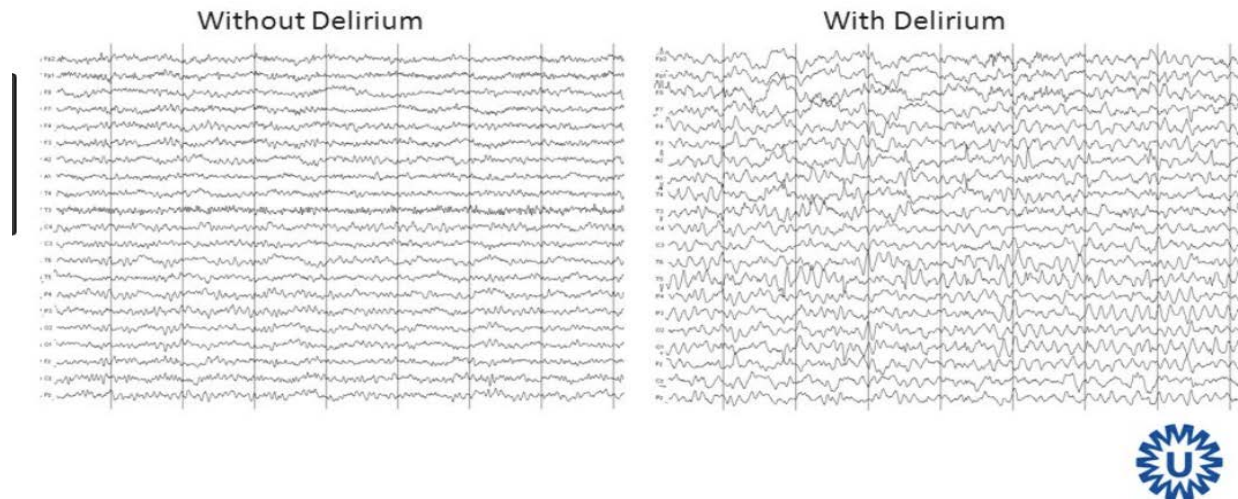
Figure 4. EEG waveforms with and without delirium.

Note: EEG waveforms with and without delirium. Reprinted from van der Kooi, W. (2015). Delirium detection in the intensive care unit [PowerPoint slides]. Retrieved from https://slideplayer.com/slide/2832681/. Reprinted with permission.

Limited-Lead Signal Processed EEG

As the science related to EEG increased, researchers began to investigate which leads (or locations of leads) were needed to detect various pathological states to reduce the number of leads required for monitoring. Additionally, scientists have begun to develop algorithms to process the EEG data and, therefore, detect meaningful changes consistent with specific conditions and disease states, including delirium. This has since led to a reduction in the number of leads required to monitor some conditions, such as level of awareness and wakefulness.

As limited lead devices have become readily commercially available, the technology regarding EEG electrodes and their application have also improved. Advancements in technology have considerably reduced the overall cost, length of time and training needed to

apply the devices. Researchers have also developed algorithms to assess and monitor for changes in EEG waveform and alert clinicians (M. A Mulkey et al., 2019). Today, nurses and anesthesia regularly use commercially available limited lead EEG devices to monitor the level of patient sedation level and depth of anesthesia (Mulkey & Everhart, 2020; M. A. Mulkey, D. E. Everhart, S. Kim, et al., 2019). Therefore, using this newer technology, limited leads with machine processed EEG may also provide a viable option for routine delirium EEG monitoring.

Plaschke et al. (2007) used a two-bipolar-electrode derivation to determine EEG characteristics that show large differences between patients with and without delirium while also discriminating delirium from other causes. In 2015, van der Kooi et al. investigated the EEG to determine which leads detect delirium the best to allow reduction in the number of required EEG leads. In that study, and re-affirmed in a subsequent study, they determined that two leads, attached on the forehead between the center of the head and ear, distinguished delirium from non-delirium (van der Kooi et al., 2015). However, the researchers recommended additional blinded studies in a general ICU patient population due to study limitations.

Following on the success from van der Kooi et al. (2015) several other studies using a variety of modified two-electrode devices have confirmed identification of EEG changes consistent with delirium. Numan (2017) conducted a study to determine if Ag/AgCl electrodes applied to the head using a headband would provide the data needed to determine delirium status. Bipolar recordings from an international 10-20 EEG system were used to obtain EEG data using three derivations (See Figure 5), Fp2-Pz, T8-Pz, and Fp2-T8 (Numan, 2017).
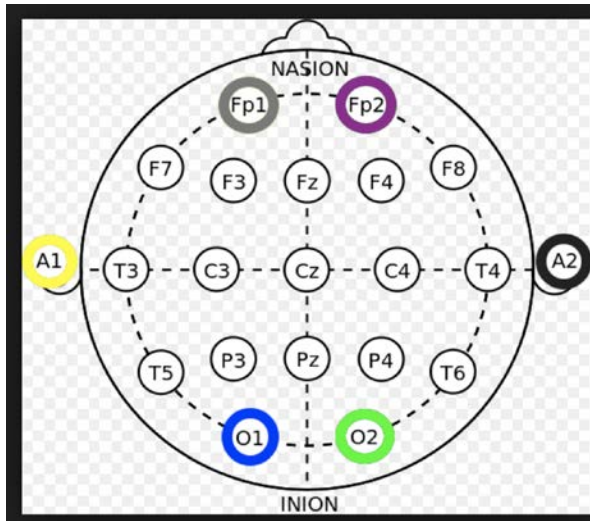
F=frontal	
P=Parietal	
O=Occipital	
T=temporal	
C=central	
Z=zero	
A=mastoid bone (reference points)	
Nasion=depressed area between the eyes just above the bridge of the nose	
Inion=crest point on the back of the head, occipital ridge	
*Numbers represent lead number: even on the right and odd on the left	

Figure 5. EEG Montage with lead site labels.

Note: Open Brain Computer Interface. (Open BCI). (2018)
Retrieved from:
http://docs.openbci.com/Tutorials/02Ganglion_Getting%20Started_Guide#ganglion-getting-started-guide-connect-yourself-to-openbci-3-view-eeg-signals. Reprinted with permission.

Based on a dichotomous classification by delirium experts – delirium and probably delirious. – several relative delta power cut-off points were examined. Using a relative delta power of 1-4 Hz, they found fair accuracy (AUC=0.75) when attempting to discriminate delirium from probably delirium. When the relative delta range was widened to 1-6 Hz accuracy improved slightly (AUC=.78). Although they deviated from the perfect discriminating test (AUC=1.00), these results were significantly better than chance (AUC=0.50). In the proof-of-concept study, accuracy of the relative delta power to discriminate between definitely delirious patients and definitely non-delirious patients was significantly higher (AUC = 0.99).

Summary

Delirium is an acute disorder of attention and global cognitive function characterized by fluctuating symptoms. Many of those who survive an episode delirium will be left with persistent

cognitive impairment. Currently, there are no effective and scalable recovery models to remediate ICU-acquired cognitive impairment.

The routine use of early delirium identification and preventive measures in the ICU is widely endorsed given the high prevalence of delirium, its deleterious effects on patient outcome, and the high costs related to these effects. The routine use of a physiologic method for delirium detection may facilitate early recognition in those patients at greatest risk at a point when interventions are more likely to be effective. Earlier detection of delirium in the older adult ICU patient population may facilitate use of early preventive strategies, but an objective physiologic objective method for delirium detection has previously been elusive.

The biochemical pathways for attention and cognition are still being characterized. Based on the prior work and the pathophysiologic mechanisms described above, evaluating the use of physiologic methods for early detection represents a major step forward in the field of delirium. Availability of continuous objective physiologic delirium monitoring will further support evaluation of individual nursing interventions and prevention strategies to determine their true effect on patient outcomes. By understanding which interventions are effective in various patient populations, nursing care can be individualized to improve the likelihood of delirium prevention and effective treatment. Unfortunately, a limited number of studies have evaluated these devices for analyzing limited lead EEG waveform for detecting delirium.

CHAPTER THREE: METHODS

This study proposed that use of an EEG algorithm will assist nurses with delirium detection in critically ill older adults. The results are an important step towards improving patient outcomes, reducing nursing workload, and decreasing overall cost of care associated with acute delirium. The pathoetiological model for delirium was used to guide this study. This delirium model describes the cellular processes that result in EEG waveform changes, why those changes occur prior to behavioral symptoms, and how they can be monitored to improve early delirium identification. Therefore, in the Methods of Identifying Neurological Delirium (MIND) study, the understanding of why patients develop delirium was used to guide sample selection, patient independent variables and potential confounders (M. A Mulkey et al., 2019).

The conventional EEG biomarkers needed for delirium detection have been identified and extracted from EEG signals obtained during monitoring using a commercially available limited lead EEG device. Plaschke et al. (2010) and others have detected significant differences in theta, alpha and beta frequencies between individuals with delirium compared to those without delirium using a two lead device with a preprogramed proprietary algorithm compared to conventional EEG but were unable to rule out other causes (Renna et al., 2003). Additionally, when using artifact-free high-quality waveform data, delirium-related changes were seen even when patients are sedated. A three-way interaction analysis confirmed there is a reduction in faster and an increase in slower frequencies (van der Kooi, Slooter, et al., 2014; van der Kooi et al., 2015) If so, these monitors may be capable of identifying delirium using limited lead using an algorithm to process EEG, thereby allowing nurse monitoring to capture of delirium's dynamic nature. This may also allow for monitoring patients who cannot participate in an

interactive assessment, such as the CAM-ICU, thereby providing expanded capabilities for delirium monitoring

Capacity Building and Community Support

A relationship has been established with key personnel at Vidant Medical Center (VMC) in (Greenville, NC) to support this research. The Senior Director for Research and the Administrator for Critical Care Services provided a letter of support. The Critical Care Clinical Nurse Specialist was a sub-investigator and provided site visits to both ICUs and discussed data collection as well as monitor storage and cleaning processes. The primary investigator attended medical staff faculty meetings to discuss the proposed research. This resulted in full provider support with all cardiac, medical and surgical critical care physicians signing an agreement permitting recruitment of their patients into the proposed study. Subsequently, cardiac, medical and surgical ICU medical directors also provided letters of support (See Appendix C).

Design

This University Medical Center Institutional Review Board (UMCIRB) approved study used a prospective, correlational design and observational convenience sampling to evaluate feasibility of using the Ceribell (Hobbs et al., 2018; M. A Mulkey et al., 2019) device (commercially available EEG) to monitor for delirium (See Appendix A). Therefore, building on prior research, this proposed feasibility study also sought to explore relationships between limited-lead signal processed EEG waveform analysis and delirium status based on CAM-ICU status in aged (≥50 years old) cardiac, medical, or surgical ICU populations requiring mechanical ventilation (Plaschke et al., 2010; van der Kooi et al., 2012a; van der Kooi et al., 2015). Specifically, the aim was to determine whether EEG waveform ratios (sleep waves:

awake waves) increase when the CAM-ICU is positive for delirium in older cardiac, medical, and surgical ICU patients (M. A Mulkey et al., 2019).

Setting

Vidant Medical Center (Greenville, NC) was selected as the clinical site for this research because improving delirium detection was a strategic priority. Additionally, ICU nurses already had prior experience using limited-lead monitoring for sedation assessment. Vidant Medical Center is an 861-bed Magnet® tertiary care, level 1 trauma, academic medical center with an office of research in support of this study. The hospital has 72 cardiac, medical and surgical ICU beds with an annual average daily census of 37.08 and average length of stay for patients requiring mechanical ventilation of 11.94 days. The ICU patient population is diverse with approximately 44% female, 56% male, 52% Caucasian, 45% African American, 2% Hispanic and 1% Native American Indian, reflecting the population of eastern North Carolina.

Sample

Although this dissertation was not powered to test efficacy, a sample of 20 participants was determined based on power analysis to be sufficient to demonstrate a moderate Cohen's effect size with 60% power. The power analysis was done using the following assumptions: 80% of enrolled participants would develop delirium with a 10% attrition rate based on prior published pilot studies (Evans et al., 2017; Vacas et al., 2016). Twenty unique participants being monitored for four days could provide as many as 80 individual assessments. This would allow for 80 potential paired CAM-ICU and EEG observations. Anticipating a 10% attrition rate and approximately 80% of enrolled participants developing delirium during the monitoring period, it was assumed that approximately 15 participants (50 paired assessments) would screen positive for delirium providing enough data for a valid analysis (Evans et al., 2017; Vacas et al., 2016).

Inclusion/exclusion criteria were chosen based on prior delirium EEG research. Inclusion criteria: 1) Medical-surgical ICU admission within the previous 24 hours; 2) Age $\geq$ 65 yrs.; 3) Requires mechanical ventilation. Exclusion criteria: 1) RASS score $\leq$ -3; 2) Patient/LAR does not speak or understand English; 3) Documented evidence or high risk for receptive aphasia (left MCA infarct or left temporal lobe tumor); brain cannot receive and analyze incoming information; 4) Diagnosis of acute brain injury (symptom onset <72 hours); 5) Documented or suspected seizure within the previous 24 hours; 6) Diagnosis of dementia; 7) Provider-planned mechanical ventilator weaning within the next 12 hours. For those meeting study criteria, the patient and/or their LAR were approached for consent (See Appendix F). Once consent was obtained, the patient was enrolled in the study.

Protection of Human Subjects

An ECU/VMC shared IRB approval was obtained. Because this study examined changes related to delirium status within a small sample, it is necessary to maximize opportunities to assess participants with delirium. Sample selection criteria included known risk factors, such as, older age, critical illness and mechanical ventilation to increase the likelihood that participants would develop delirium during the enrollment period. To interpret valid patient responses and delirium status, those with aphasia and those who did not speak or understand English were excluded. Acute brain injury, dementia and recent seizure activity may confound EEG data, potentially limiting interpretation and were therefore exclusions.

Critically ill mechanically ventilated older adult patients are a vulnerable population. Several previous studies utilizing limited-lead EEG monitoring and examining delirium in older critically ill patients have been conducted with no serious adverse events (Plaschke et al., 2010; Renna et al., 2003; Siddiqi et al., 2016). To support informed consent, LARs provided consent

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when participants lacked decision-making capacity; this was consistent with IRB protocols for the recruitment site. Capacity was determined by talking with the care nurse prior to approaching the patient to determine level of orientation and use of sedating medications. Just prior to consenting, patients were asked two questions: 1) "Where will the sensors be applied?" and 2) "How many days will you be in the study?" If these were answered correctly and the patient could sign consent forms, the patient provided written consent. If the patient could not accurately answer questions and sign consent forms, consent was obtained from the LAR. Patients not able to provide consent were provided opportunity to provide assent each day.

Data were downloaded directly into REDCap requiring investigators to log in each time it was accessed. Data included for statistical analysis were substantively de-identified; however, medical record numbers were included on a separate spreadsheet in a separate folder accessible only to the investigator and ECU primary mentors. The purpose for including MRNs was to link data with participants for data accuracy validation. Only aggregated data on the research drive were available to additional research team members.

No attempt was made to identify or contact participants after they were discharged from the critical care unit. No direct benefit was anticipated for participants. However, delirium is a common concern, especially in geriatrics. While this study did not provide direct benefit to participants, if an association between EEG waveform analysis and delirium status was identified, the increased sensitivity would allow earlier, accurate detection of and individualized nursing interventions across future adult patient populations.

Recruitment and Retention

To prevent a cold contact, the bedside nurse determined the patient and/or their LAR's interest in research participation. If interested, the primary investigator provided the participant

and/or their LAR with an introduction to the study along with a research information sheet (See Appendix G). With 80% of aged ICU patients presumed to develop delirium and VMC having approximately 40,000 patient days and 13,000 ventilator days from 3,500 unique patients annually, a six-month data collection period was anticipated and would require enrollment of one participant each week. A member of the research team was on site each day to consent eligible participants.

Implementation

Vidant Medical Center's biomedical department ensured Ceribell monitors met hospital standards. Recruitment was based on monitor availability. Because sensors needed to be reapplied each day, sensor sites were marked for placement. Marking sensor sites increased reliability of EEG data collection. Daily equipment quality checks occurred one hour prior to CAM-ICU assessment (Appendix H). The CAM-ICU assessments occurred each day based on RASS score to minimize sedation effects on the CAM-ICU score. The RASS is a 10-point Likert type scale with scores ranging from unarousable (-5) to combative (+4). Patients who are calm and alert score a zero (Boettger et al., 2017; Haenggi et al., 2013). Weekly interrater reliability checks with the neuropsychologist enhanced fidelity of measurement (See Appendices A & B).

Research Instruments

Confusion Assessment Method-Intensive Care Unit

To improve the accuracy of assessment of nonverbal and restrained patients, modifications were made to the original CAM tool based on the DSM IV delirium criteria. This new assessment, the CAM-ICU, developed by Ely, Margolin, et al. (2001) is the most validated delirium assessment tool with a sensitivity of >90% and reliability of k >0.79 when used by researchers (van Eijk et al., 2011). Patient characteristics were collected from the electronic

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medical record (EMR) and Social Security Death Index allowing quantification of illness severity and mortality (See Appendices H & I). EEG waveforms were collected using a limited-lead EEG monitoring device, the Ceribell. EEG waveform analysis was conducted using MATLAB with Higher Order Signal Analysis and Fieldtrip toolbox functionality.

The CAM-ICU was originally validated with the DSM-III and later determined to be consistent with the DSM-IV criteria. The CAM-ICU is an interactive assessment with four components corresponding to the key features of delirium: 1) acute onset or fluctuation in mental status within previous 24 hours; 2) inattention; 3) altered level of consciousness (RASS ≠ 0) and 4) disorganized thinking (Boettger et al., 2017; Haenggi et al., 2013).

Conducting the CAM-ICU

The CAM-ICU takes approximately 2–3 minutes to complete and can be easily incorporated into nurse and physician daily routines, making it a reasonable option for delirium assessment in the ICU (Schuurmans et al., 2003). Instructions on use of the CAM-ICU are standardized and interrater reliability is enhanced after training (Blevins & DeGennaro, 2018). A training video is available at http://www.icudelirium.org/delirium/monitoring.html. To complete a CAM-ICU assessment the patient must be alert enough to participate in the assessment. Altered level of consciousness is determined based on the RASS score. The RASS is a 10-point scale assessing level of sedation and agitation. Scores range from unarousable (-5) to combative (+4) (Boettger et al., 2017; Haenggi et al., 2013).

Inattention was determined based on the number of errors that occurred when having the patient squeezed the examiner's hand each time the examiner said the letter "A." Disorganized thinking was assessed by asking the patient to answer four yes/no questions and to complete a two-step command. A positive delirium assessment included acute onset or fluctuating mental

status (Feature 1) and inattention (Feature 2) plus either altered level of consciousness (Feature 3) or disorganized thinking (Feature 4). Therefore, if the patient had both of the first two features and either feature three or feature four, they were deemed positive for delirium.

Table 3. Summary of studies CAM-ICU Compared to DSM-IV

First Author	Year	ICU Population	Sample	Sensitivity	Specificity	NPV	PPV
Boettger, S	2017		210	50%	95%		
Ely, W	2001	Medical & Cardiac	96	93-100%	98-100	98-100	92-100%
Ely, W	2001	Medical	38	95-100%	89-93%		
Gusmao-Flores, D	2012	Mixed	969	77.1- 82.6%	95.9%		
Han, J	2014	ED	406	72.-68.0%	92 -98.6%		
Koga, Y	2015	Surgical	99	78-97%		94-97%	83-88%
Plaschke, K	2008	Surgical	174			8%	11%
Shi, Q	2013	Mixed	1409	81%	98%		
van Eijk, M	2009	Mixed	126	64%	98.1	83%	94.6%
Vasilevskis	2010	Mixed	3846	0.81	0.81		

Table 4. Summary of studies CAM-ICU Compared to ICDSC

First Author	Year	ICU Population	Sample	Sensitivity	Specificity	NPV	PPV	Intertest
Boettger	2017		210	50%	95%			*k*=.56
Fagundes	2012	Medical Surgical & ED	595					*k*=.5
McNicoll	2005	Medical	22	73%	100%	64%	100%	
van Eijk	2009	Mixed	126	64%	98.1	83%	94.6%	

Accuracy

Sensitivity and positive predictive value (PPV) are important for determining the accuracy of a positive test while specificity and negative predictive value (NPV) reflect the accuracy of a negative test (Ryan-Wenger, 2017). Concurrent validity was evaluated by having a psychiatrist, neurologist, geriatrician or nurse assess patients using DSM criteria. Many of the studies reported results as binary (yes/no) and, therefore, discuss the Cohen's kappa coefficients as a means of removing agreement obtained simply by chance (Ryan-Wenger, 2017). Because several of the studies had small sample sizes that could have resulted in falsely low agreement, investigators also reported confidence intervals allowing the reader to discern meaningful versus potentially false results (See Table 2). Eighty percent of studies used a 95% confidence interval (55-100) and found statistically significant results (McNicoll et al., 2005; Truman & Ely, 2003). Because results were binary as opposed to ordinal or interval, none of the studies described used an intraclass correlation, Lin's concordance correlation coefficient, Bland-Altman plots, or absolute differences (Ryan-Wenger, 2017).

Fifteen studies compared the CAM-ICU as a whole to the DSM III to assess the tool's overall agreement with the American Psychiatric Association's definition (American Psychiatric Association, 1987; Ely, Gautam, et al., 2001; Ely, Inouye, et al., 2001; Ely, Margolin, et al., 2001). In those studies, overall accuracy was high (78-87.5%) with high specificity (Adamis et al., 2012; Koga et al., 2015; McNicoll et al., 2005; McNicoll et al., 2003; Truman & Ely, 2003). While high sensitivities and specificities were found in most studies, one study found a sensitivity of 37% (95% CI 29-37) (Ely, Inouye, et al., 2001; Ely, Margolin, et al., 2001; Gusmao-Flores et al., 2012).

Two studies compared individual features or components of the CAM-ICU with the DSM III. While there was good overall internal consistency with a Cronbach's alpha of 0.84 (95% CI 0.77-0.89), there were inconsistencies in feature one, acute onset or fluctuating course (Adamis et al., 2012; Koga et al., 2015). On feature one, Adamis et al. (2012) determined the k coefficient to be .83 (CI 95% .0-.96) while Koga et al.'s (2015) k coefficient was .22 (CI 95% (.03-.41). Koga and colleagues described potential causes, including nurses having difficulty assessing patients and lack of nurse motivation.

Inter-rater reliability has been evaluated in a variety of ICU populations as well as sample populations of persons >65 years, those with dementia and based on APACHE (acuity) scores. Initial reliability testing completed by Ely, Margolin, et al. (2001) found overall CAM-ICU agreement between nurses and intensivists was high (Ely, Inouye, et al., 2001; Ely, Margolin, et al., 2001). Multiple studies have found excellent interrater reliability between nurses, and between nurses and intensivists (Ely, Inouye, et al., 2001; Ely, Margolin, et al., 2001; Haenggi et al., 2013; Miyazaki et al., 2011; Terry et al., 2015; Tomasi et al., 2012). Because delirium is dynamic with behavioral symptoms changing throughout the day, intra-rater reliability is not a meaningful statistic and therefore not reported. Some limitations were thought to include time and sedative administration between assessments.

Plaschke et al. (2008) conducted a study to determine consistency in agreement between the CAM-ICU and ICDSC throughout participants' first week of ICU admission (See Table 3). Because the ICDSC is a retrospective evaluation over the previous 24 hours, while the CAM-ICU is a point in time assessment, analysis consisted of evaluating behaviors likely to contribute to inaccurate results. The k coefficient over a seven-day period and by each day individually indicated agreement between the two assessment methods (Plaschke et al., 2008).

CAM-ICU in relevant populations

When evaluating participants based on age, older participants' (≥65 years) assessments had substantial agreement (*k*=68-100). In a subgroup analysis of participants ≥65 years, interrater reliability across groups reflected *k* values of 0.92 (Ely, Margolin, et al., 2001). However, conflicting results were found in a subsequent study looking specifically at older patients in the emergency department where agreement was <90% even when patients having a neurological diagnosis (n=32) were excluded (Han et al., 2014).

A systematic review conducted by Gusmao-Flores et al. (2012) of pooled sensitivities found a 75.5% sensitivity with no significant differences when comparing subgroups according to age, suspected dementia, and severity of illness. There were also no differences in *k* scores between medical and surgical patients after accounting for differences in acuity (Fagundes et al., 2012). However, significantly higher *k* scores were found in patients with APACHE II acuity scores ≥ the median value of 23 (Fagundes et al., 2012). When comparing rater agreement based on the need for mechanical ventilation, interrater reliability was highest in patients requiring mechanical ventilation (*k*=96-100).

Researchers analyzed whether higher levels of sedation led to false positives on the CAM-ICU. They found moderately sedated participants were more likely to have a positive CAM-ICU (van Eijk et al., 2009). Another study found little difference (3%) in delirium identification between CAM-ICU and a reference standard in patients who were mild to moderately sedated (able to make eye contact and follow commands; RASS scores = -2 to -3), while other studies identified a significant impact on accuracy when based on level of sedation (Ely, Inouye, et al., 2001). Prevalence rates decreased from 53 % to 31% (CI 95% 54-27, p < 0.001) when patients with lower RASS scores (more sedated) were removed (van Eijk et al.,

2009). Similar findings were present even after stopping sedative infusions (delirium vs. persisting sedation). Investigators determined 58% of patients were insufficiently vigilant to follow instructions and therefore unable to be assessed at a RASS score of -2 to -3, (van Eijk et al., 2009). When initial RASS scores were -4 to -5, meaning deeply sedated to unarousable, even after stopping sedation, 23% of participants remained moderately sedated (RASS -2 to -3). Eighty-nine percent of altered or lethargic patients could be evaluated once alert.

In exploring mixed models, there was a 45% probability of delirium when all positive CAM-ICU assessments were included. When the 20% of patients with RASS scores of -2 to -3 (moderately sedated) were excluded, 29% of patient assessments were considered to be insufficiently vigilant to follow the instructions (van Eijk et al., 2009). Eleven percent of subjects continued to be unable to follow commands and were therefore not testable (Brown, Fordyce, et al., 2011). As a result, authors concluded that sedation significantly increased the likelihood of a delirium-positive CAM-ICU.

In several studies, accuracy of the CAM-ICU was lower in patients with mild delirium (30%), baseline mild cognitive impairment (33%), and dementia (62%) as opposed to patients without cognitive impairments (Schuurmans et al., 2003; Shi et al., 2013; van Velthuijsen et al., 2016). While assessments could not be completed in half of the patients because of severity of cognitive impairment, one study found patients with suspected dementia had significantly higher rates of agreement (100%) with k=0.96 (95% CI, 0.92-0.99) (Brown, Fordyce, et al., 2011).

Five studies have compared sensitivity between delirium subtypes (hypoactive, hyperactive, and mixed). These studies consistently found significantly lower (31-64%) sensitivities in patients with hypoactive delirium (Han & Wilber, 2013; Lin et al., 2015; van Velthuijsen et al., 2017).

Limitations

When clinicians use the CAM-ICU in the clinical setting, accuracy decreases

significantly. There are several distinct differences when comparing psychometric testing with

implementation research. The intent for use in the clinical setting was to determine if an

individual patient was delirious, not to evaluate performance of the tool. In the research setting,

screening results are determined based on congruence of assessments between those performed

by a limited number of individuals with similar training, expertise, and recent education.

However, in the clinical environment, there are many individuals performing assessments. Tool-

utilization training is often limited and sometimes occurs a significant time prior to using the

tool.

Swann et al., (2014) and Terry et al., (2015) determined that the CAM-ICU requires

extensive and frequent training to obtain and maintain high interrater reliability. Implementation

research has shown these limitations lead to low sensitivity and poor interrater reliability at 43-

47%, meaning the CAM-ICU appropriately detected delirium less than half of the time (Mulkey,

Hardin, Olson, et al., 2018; Soja et al., 2008). This was thought to be a significant challenge in

the critical care setting where nurse turnover rates are likely to be greater than 20% annually.

Delirium assessments include subjective measures that lead to interpretation bias and,

therefore, pose a challenge. These challenges were found while using the RASS to determine

level of consciousness and interpretation of baseline and fluctuating cognitive status.

Weaknesses in the tool related to acute onset or fluctuating symptoms were likely because, in the

setting of critical illness, it was not clear to raters when the onset of symptoms began (Koga et

al., 2015). "Acute" is interpreted differently across raters. This likely results in inaccurate use of

the tool and dismissing results assumed to be due to another cause, such as dementia and depression.

The CAM-ICU performs best in nonverbal patients receiving minimal or zero sedative medications (RASS score of > -2) as reflected in the van Eijk et al. (2009) study. When sedation levels increased to a RASS score of ≤ -2, more than half of participants had inaccurate assessment findings or were not able to be assessed. Of particular concern in older (>65 years) adults, accuracy is significantly lower (31-64%) in patients experiencing the hypoactive subtype (Han et al., 2017; van Velthuijsen et al., 2017).

In a sample of 116 patients reviewing a total of 906 individual CAM-ICU documentation opportunities, Terry et al. (2015) found 48% of assessments inaccurately reflected delirium status and another 30% of assessments were inappropriately identified as "unable to assess" (UTA). These inaccuracies were equally divided between false positive and false negative findings. In 2014, Swan et al. conducted a quasi-experimental study to determine if education would decrease the frequency of inappropriate UTA when nurses document. Their theory was that reducing the frequency of inappropriate CAM-ICU ratings (ratings were not accurate) would improve the accuracy of nurse delirium detection. Baseline findings showed that 32% with an odds ratio of 30.7 (95% CI, 8.9-105.9; $p < .001$) CAM-ICU assessments were inappropriately documented as UTA (Swan, 2014). Sixty-three percent (27 out of 43) of inappropriate assessments involved patients requiring mechanical ventilation or the hypoactive subtype (Swan, 2014). Providing education reduced the UTA frequency to 19%, reflecting a need for ongoing training to maintain accuracy of nurse assessments (Swan et al., 2011).

Usefulness in proposed research

Despite limitations, the CAM-ICU is considered an acceptable standard and the only screening tool validated in both geriatric and ICU patient populations. Therefore, the CAM-ICU was the best option for determining delirium status in comparison with EEG data. If signal processed EEG data accurately identified delirium in critically ill patients, this would potentially allow for assessment of the 58% of patients currently not accurately assessed.

Ceribell

The Ceribell is a relatively new technology. Ceribell was developed by Ceribell, Inc. and received FDA approval in 2017 (Ceribell Inc., 2018). The device uses a 10-electrode system housed in an elastic headband to monitor EEG (See Figure 4). The electrode montage includes: Fp1-F7, F7-T3, T3-T5, T5-O1, Fp2-F8, F8-T4, T4-T6, T6-O2. Ceribell collects data at a frequency rate of 250 Hz and uses built-in high- and low- pass filers to eliminate frequencies less than 0.5Hz and greater than 30Hz (See Figure 6). Therefore, the collection frequency rate (250 Hz) was high enough to obtain the desired data. Data were then transmitted over Wi-Fi to the Ceribell portal and stored in one patient file for later remote viewing and analyzing.

Figure 6. Ceribell Device

Note: Provided by Ceribell, Inc.

To increase likelihood of recording high quality data, a system check was needed prior to each data collection period (Malissa A Mulkey et al., 2019). The system check included

verifying correct application and location of the headband and electrodes and checking the impedance level. If the impedance was high, there would be a lot of noise in the EEG data and, therefore, artifact. The Ceribell has a stethoscope that provides an audible depiction of EEG waveforms, similar to the sound heard during a cardiac echocardiogram. Observation of the EEG waveforms on the Ceribell screen can be used to evaluate the quality of data collected. If there was high impedance or poor-quality waveforms on the EEG screen, evaluation for loose cable connections, patient movement, and the need to insert electrode gel into the electrode housing was needed. The Ceribell device has an indicator for each electrode site that lights up red when connections are impaired.

Data Collection

Prior to participation, all participants or their LAR signed a written consent. Once enrolled, a Ceribell headband was applied to each participant's head by the primary investigator. Sensors were connected by the primary investigator to the Ceribell monitor and a CAM-ICU assessment was performed by the primary investigator. Completion of a system check by the primary investigator including assessment of sensor connections and EEG waveform quality occurred each day (See Figures 6 & 7). Troubleshooting EEG monitors were conducted by the primary investigator using industry standards.
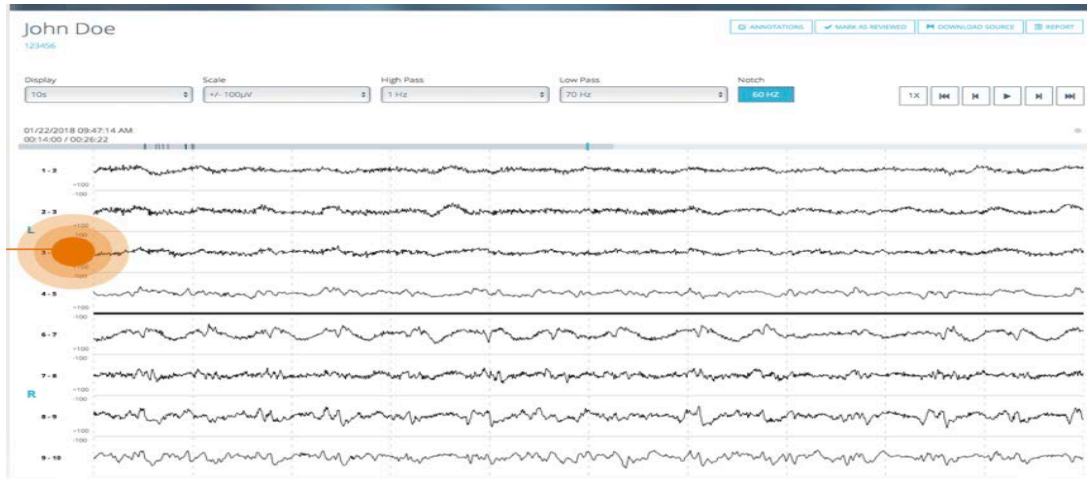
Figure 7. Ceribell EEG screen.

Note: Provided by Ceribell, Inc. https://ceribell.com

Once all checks were completed and the patient had a RASS score of -2 or higher, the primary investigator performed CAM-ICU assessments on each participant and documented findings on a case report form in REDCap. The primary investigator collected subsequent CAM-ICU and EEG data each day during a four-day window. EEG and CAM-ICU data were recorded by the primary investigator as a dichotomized value and coded as delirium present or delirium absent.

Missing Data

Only data from paired observations, CAM-ICU and high-quality EEG data for each observation, was included in the analysis. Each paired assessment (CAM-ICU + EEG) was considered a separate observation. For participant who withdrew from the study, available data were included in the analysis. Analysis was completed using individual observations rather than unique patients.

Data Management

EEG monitor data were saved to the CLOUD and downloaded as an analog file daily on the secure password-protected research drive. Files were then uploaded as a .csv file to a server

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using Microsoft import feather with | as delimiter and downloaded into MATLAB for analysis (MathWorks Inc., 2012). Patient demographics, EMR and administrative data were uploaded into REDCap as a .csv file (Harris et al., 2009).

EEG Analysis

MATLAB analysis was executed using the Higher Order Signal Analysis toolbox function. Bergen plugins removed artifact during analysis. EEG data with artifact were not analyzed. Hamming windows were then be applied to reduce variabilities. The power of different frequency components was then calculated by estimating the periodogram of the signals. Analysis of 5-minute epochs were completed to get a range (min, max) and median. The periodograms meeting quality specifications closest to the time of the CAM-ICU assessment were used for statistical analysis. Theta/alpha ratios were evaluated and considered positive for delirium if the ratio is ≥2.

Data Analyses to Answer Research Questions

Statistical analyses were performed using SPSS software (version 24 or higher) (IBM Corporation, 2016). Descriptive statistics were used to summarize patient demographics and clinical characteristics, including known risk factors, and theta/alpha and delta/alpha ratios based on delirium status (positive or negative) (See Appendix G & H).

Known risk factors were: age, race, gender, marital status, living situation, insurance type, drug and alcohol use, comorbidities, admission diagnosis, GCS score, APACHE mean score, ICU length of stay and hospital length of stay. To determine representativeness of the sample, the relationship between study variables and delirium status was examined by conducting independent t-tests for continuous variables and chi square analysis for categorical variables. To examine whether a difference in defining EEG characteristics existed in those individuals

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admitted to the cardiac, medical, or surgical ICU who developed delirium compared to those who did not develop delirium independent t-tests for continuous variables and chi square analysis for categorical variables were conducted. Evaluation of delirium's impact on hospital discharge disposition and 30-day mortality (alive/deceased) were completed using chi square analysis. The theta/alpha ratio and delta/alpha ratio were compared with delirium status under two conditions: delirium positive and negative. Visually this was done using side-by-side boxplots. To determine if there was a relationship between theta/alpha ration or delta/alpha ration and delirium status determined by the CAM-ICU independent t-tests were used to examine both ratios as a continuous variable and chi square as a categorical variable. Numeric summaries were reported along with two sample t-tests. Chi-square analysis was used to explore comparisons between the theta/alpha ratio (<2 or ≥ 2) and CAM-ICU delirium status positive or negative (van der Kooi, 2014). Matthew's (or phi) or phi correlation coefficient (MCC) and a 95% confidence interval were used to explore relationships between EEG-determined delirium status and CAM-ICU delirium status. MCC is an autonomous statistic (geometric mean corrected for chance agreement) that provides a balanced measure considering true and false positives and negatives. Because the CAM-ICU and EEG data were obtained as a paired assessment, individual patients were used as their own control. Therefore, it was not necessary to adjust for confounders as EEG and CAM-ICU are independently assessed on the same patient. A theta/alpha ratio ≥ 2 with a moderate effect size in patients with delirium were deemed sufficient to propose that EEG from a limited lead montage is an adequate biomarker for delirium. Additionally, a within and between subjects' analysis were conducted to assess trends and changes over a four-day period. Because assessments were repeated, to address the possible effects, mixed effects models were used. Changes in rates and proportion each day were assessed using McNamara's test (McCrum-

Gardner, 2008). Control for potential confounding variables and patient differences, such as medication and severity of illness, were addressed during between group analysis with a general linear model for continuous variables and logistic regression models for categorical variables (van der Kooi, 2014). To address differences in the number of assessments between participants random effects models analyses were undertaken.

Potential Limitations and Alternative Approaches

Although only 17 unique participants were recruited, assessing each participant over a four-day period provided an opportunity to obtain 80 paired CAM-ICU and EEG observations. Assuming a 10% rate of attrition, it was anticipated 18 of consented participants would complete all four days. Therefore, approximately 70 paired assessments should provide ample data for pilot testing of specific aims. Monitors could have failed to record data, preventing assessment. If a monitor failed to collect data, it was removed and replaced with another approved monitor. Technical problems or artifact (poor signal quality or increased patient muscle activity) could occur. A 2-hour window was selected to allow opportunity to obtain 5-minute periodograms of high-quality EEG data. Sensor locations were also marked when applied to promote consistency in data collected. Applying Ceribell monitors for the purpose of this study was outside the institutions usual care. Similar limited-lead EEG monitors were used routinely for intubated patients requiring sedation and neuromuscular blockade at many institutions across the globe, including VMC. Risks associated with Ceribell monitoring were minimal and confined to local skin irritation. Any interruption in skin integrity resulted in exclusion from further monitoring.

Next Steps

Although this study was a trial to refine the identification of appropriate delirium biomarkers, it may provide a foundation to incorporate EEG-based cognitive monitoring into

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acute care settings for those who are at highest risk of delirium, critically ill older adults (>64 years). The findings of this research were expected to test the efficacy of the research protocol and provide feasibility data for a larger study validating limited-lead signal processed EEG sensitivity and specificity for delirium detection. Going forward, the findings may be expanded in several ways. A sub-analysis could assess Ceribell-derived data changes over time for patients who develop delirium. A larger study may help decide device usefulness for determining appropriate prevention and treatment strategies to decrease morbidity and mortality, improve patient outcomes, and reduce cost of care. Future studies may potentially eliminate the need for frequent intermittent nurse delirium assessments by providing an objective method to ascertain which nurse-driven interventions are most effective in preventing and treating delirium. A new diagnostic tool for this purpose should increase sensitivity to >50% to improve our current recognition of delirium.

Use of limited lead EEG using a commercially available device, the Ceribell, is innovative in several aspects. First, this was the first study in geriatric ICU patients using a 10-lead signal processed EEG device capable of collecting data from all 6 lobes of the brain based on plausible pathophysiologic pathways. Collection of these biomarkers provided valuable neuroelectrical data to better understand the pathophysiology associated with increased risk for long-term cognitive impairment in survivors of ICU delirium and potential therapeutic targets for future studies. Most importantly, this study will pave the way for a large effectiveness trial to test accuracy and clinical significance of EEG data derived from this 10-lead device.

Although prevalence was high, multiple studies reported that in clinical practice, more than 75% of patients with delirium were missed using currently available clinical delirium screening tools such as the CAM-ICU. Importantly, the diagnostic process as we know it today is closely

tied to the clinical experience of the clinical team caring for the patient. In this context, the precision medicine initiative has highlighted that objective disease markers, biomarkers, are key to guiding individualized approaches to patients in order to improve individual outcomes. Such biomarkers are yet unavailable in delirium, posing an explanation for the current lack of a standardized approach.

This study represents an innovative approach for nurses to detect delirium. Using EEG with a limited number of electrodes and automatic processing may offer an objective tool to detect a cause for the encephalopathy that underlies delirium. Patients in the ICU are monitored for various physiologic alterations. Consequently, EEG-based detection of delirium may fit better in the local culture than cognitive testing and is no longer cost prohibitive. Therefore, processing the EEG wave frequency and power analysis into a new value could provide a cost effective, feasible method for early continuous objective delirium assessment that is better than current methods.

CHAPTER FOUR: DETECTING DELIRIUM USING A PHYSIOLOGIC MONITOR MANUSCRIPT

Abstract

For the past 2500 years, delirium has been described based on the presence of behavioral symptoms. Each year as many as one in five acute care and 80% of critically ill patients develop delirium. The United States spends approximately $164 million annually to combat the associated consequences of delirium. There are no laboratory tools available to assist with diagnosis and ongoing monitoring of delirium, therefore, current national guidelines for psychiatry, geriatrics, and critical care strongly recommend routine bedside screening. Despite the significance, healthcare teams fail to accurately identify approximately 80% of delirium episodes.

The utility of conventional EEG in the diagnosis and monitoring of delirium has been well established. Neurochemical and the associated neuro-electrical changes occur in response to overwhelming stress prior to behavioral symptoms, therefore, using EEG will improve early delirium identification. Adding EEG analysis to the current routine clinical assessment significantly increases the accuracy of detection. Using newer EEG technology with a limited number of leads that is capable of processing EEG may provide a viable option by reducing the cost and need for expert interpretation. Because EEG monitoring with automatic processing has become technically feasible, it could increase delirium recognition. EEG monitoring may also provide identification prior to symptom onset when nursing interventions would be more effective, likely reducing the long-term ramifications. Having an objective method nurses can easily use to detect delirium could change the standard of care and provide earlier identification.

Delirium

For the past 2500 years, delirium has been described and understood based on the presence or absence of behavioral symptoms (Adamis et al., 2007). Not until 1983 was there an agreed upon definition when the American Psychiatric Association (APA) published the 3rd edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM). The APA, in the DSM, defines delirium as "primarily a disturbance of consciousness, attention, cognition, and perception that can also affect sleep, psychomotor activity, and emotions." Since that time, DSM criteria have been revised several times, with the most recent being the DSM-5.

A growing body of literature demonstrates the significance of delirium in terms of mortality, reduced quality of life and increased cost of care. Each year hospitals are faced with as many as one in five acute care and 80% of intensive care units patients developing delirium (Oldham et al., 2017). As a country, the United States spends approximately $164 million annually to combat the consequences associated with delirium (Bail et al., 2015). This amount is expected to increase dramatically over the next 20 years as the percentage of adults older than 65 years of age increases. This increase will result in an estimated one in four individuals falling into this age bracket.

Unlike many psychiatric conditions, there are no laboratory tools available to assist with diagnosis and ongoing monitoring of delirium (Koponen et al., 1989). Researchers have developed and evaluated more than 40 different clinical assessment tools and published more than 800 articles to assist clinicians in identifying the presence of delirium (Garg et al., 2018). The current standard for diagnosis is a clinical examination including criteria from the DSM-V (American Psychiatric Association, 2013). Their criteria are included in Table 1.

Table 5. DSM-V Criteria for Delirium

Diagnostic and Statistical Manual – 5
Disturbance in *attention* (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced *orientation to the environment*)
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.
An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).
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*
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*.

Current national guidelines for psychiatry, geriatrics, and critical care strongly recommend routine screening for delirium. While there are several systematic reviews describing ICU delirium screening tools, to date, there is no single review of available geriatric screening tools. Due to lack of enough evidence, neither the American Psychiatric Association nor the American Geriatric Society have recommended a particular tool for delirium screening. Although numerous delirium assessment tools are utilized in hospitals, there remains tremendous

subjectivity with such approaches. This subjectivity results in failure of nurses to identify as many as 80% of delirium cases (Inouye et al., 2001).

In 2013, the Society of Critical Care Medicine (SCCM) published the *Pain, Agitation, and Delirium Guidelines* recommending use of a validated tool for routine delirium screening. Although a definition for routine is not defined, two critical care screening tools were recommended: The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) for delirium screening.(Barr et al., 2013b) Both tools are clinical assessments to detect the behavioral symptoms resulting from delirium and have been well-validated in research settings. The CAM-ICU and ICDSC have been determined to be the most valid, reliable, and feasible delirium assessment tools for use in adult ICU patients. Of these two tools, only the CAM-ICU is considered validated in both geriatric and ICU patients. The CAM-ICU is the most studied and as a result, has been described in the literature as the gold standard for assessing delirium in the ICU setting.

Despite the significance, healthcare teams fail to accurately identify about 80% of delirium episodes (Heriot et al., 2017). Delirium is often undiagnosed or mistaken for other conditions such as dementia and depression even when using a standardized bedside assessment. Some of the likely causes include the fact that delirium fluctuates throughout the day, assessments are either intermittent (usually once a shift) or retrospective over the previous 8-12 hours drawing on the clinicians recall, and components of the assessment are subjective and/or not clearly defined. Even when appropriately identified, delirium is often well established, further increasing the risk for poor long-term outcomes. Therefore, this review seeks to describe a potential alternative for identifying delirium in critically ill patients.

Delirium and bedside assessment

Implementation research has shown limitations of the CAM-ICU assessment tool lead to low sensitivity and poor interrater reliability at 43-47%, meaning the CAM-ICU appropriately detected delirium less than half of the time (Soja et al., 2008). Accuracy of delirium assessment using the CAM-ICU has been shown to be lower in patients with mild delirium (30%), baseline mild cognitive impairment (33%), and dementia (62%) as opposed to patients without cognitive impairments.(van Velthuijsen et al., 2016) In patients with hypoactive delirium, research has consistently shown significantly lower (31-64%) sensitivities (van Velthuijsen et al., 2017). Further contributing to low sensitivities, the CAM-ICU requires extensive and frequent training to obtain and maintain interrater reliability. As many as 29% of patients have been found to be insufficiently vigilant to follow the instructions to complete a CAM-ICU assessment ($p < 0.001$), even after excluding moderately sedated patients (van Eijk et al., 2009). Hypoactive delirium is more difficult to detect, resulting in significantly lower accuracy (31-64%). The high prevalence of hypoactive delirium in patients who are 65 years old or older is of particular concern for the older adult patient population. Ideally, assessment of older adults would include a measure capable of distinguishing "organic" from "functional" causes of acute mental status changes as well as differentiate delirium from dementia (Koponen et al., 1989). Organic, meaning a disturbance caused by injury or disease affecting brain tissues as well as by chemical or hormonal abnormalities. As opposed to organic, functional causes are disturbances with no known associated organic or pathological tissue changes that can be found as causes for the symptoms. Further, it is recommended the measure provide a reliable method to indicate severity of illness and retain validity with repeated use. EEG with quantitative analysis has the potential to fulfill these requirements.

Use of Electroencephalogram (EEG)

In 1875, Caton (1875) discovered the fluctuating waveforms that constitute the EEG by reflecting a beam of light on the mirror of the galvanometer. When the electrodes were placed on two points, this beam of light was directed toward a large scale placed on the wall allowing him to visualize currents of varying direction as they pass through a multiplier (p 1-2)(Niedermeyer & Da Silva, 2005)

The utility of conventional EEG in the diagnosis and monitoring of delirium has been well established since Romano and Engel's work investigating the relationship between arousal and degree of abnormality on EEG among hospitalized delirious patients (Romano & Engel, 1944) They discovered a decrease in background EEG frequency while disorganization increased. As a result, it was determined that those changes were correlated with reduced arousal. Level of arousal is the patient's overall level of responsiveness to the environment. Impairment in the level of arousal signifies the presence of an underlying brain dysfunction. Arousal is a component of many delirium assessments and level of arousal also seems to distinguish delirium from dementia. This work was extended by multiple researchers who replicated those findings, using computer based quantitative EEG analysis, or QEEG (Laidlaw & Read, 1961). Using these measures, research has shown adding EEG analysis to the current routine care and clinical assessment typically performed once or twice a day using a standardized delirium assessment tool, significantly increased accuracy to greater than 95% (p=.003) when compared with the current practice identifying about 20% of delirium (Trzepacz et al., 1992).

EEG Waveforms

EEG waveforms are generally classified according to their frequency, amplitude, shape and position on the scalp. Frequency, measured in hertz (Hz), is the basic unit used to determine

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normal and abnormal rhythms. EEG can be divided into different frequency bands. The familiar classification of waveforms, including alpha (8–12 Hz), beta (13-30 Hz), theta 4-8 Hz, delta (0.1-4 Hz) and gamma (30-100 Hz), are based on the signal frequency. EEG signals are also classified based on the frequencies for different state/stimuli (Kumar & Bhuvaneswari, 2012). Amplitude is the measure of change. Amplitude is measured from the two most extreme values. While the total range is much higher, a typical adult human EEG signal is about 10 µV to 100 µV in amplitude when measured from the scalp. Shape of the EEG waveform is assessed in terms of spikes, sharpness, phases (i.e. monophasic and polyphasic), and area of the brain or location. Certain patterns are considered normal at a specific age, state of alertness or sleep. The EEG can be used along with other measurements including eye movement or electrooculography (EOG) and finger and jaw clenching or electromyographic (EMG) to define sleep stages. EOG and EMG are considered artifact because they interfere with accurate recording of EEG. As a result, filters and other methods are routinely used to eliminate or reduce this artifact.

According to Maldonado's pathoetiological model of delirium, the evolution of delirium begins with a stress response and the resulting neurochemical impact (Maldonado, 2008). His model describes multiple cellular level cerebral processes leading to microlevel chemical changes ultimately disrupting equilibrium. The stress response and resulting disequilibrium initiates multiple cascades that become a vicious cycle of competition between supply and demand. These changes are depicted as neuro-electrical changes on EEG. When the brain can no longer compensate, the individual begins to develop the behavioral symptoms associated with delirium such as alteration in level of arousal and disorganized thinking. The pathoetiological model of delirium goes on to explain that neurochemical and their associated changes in neuro-

electrical activity in response to overwhelming stress occurs prior to behavioral symptoms, and how they can be monitored using EEG to improve early delirium identification.

One of the most prominent EEG waves is the alpha (8–12 Hz) wave, which is observed in all age groups and commonly found in adults who are awake but relaxed. In the awake state, particularly with the eyes closed, the alpha activity is maximal over the parieto-occipital lobes (Giattino et al., 2017). These waves are thought to reflect rhythmic, reciprocal interactions between the thalamus and visual areas in the occipital and parietal cortices. Functionally, awake alpha has been associated with levels of arousal, relative cortical deactivation or inhibition, and attention, and is thus an important factor in cognitive function. Measures of awake alpha have been found to be decreased in patients with cognitive deficits such as delirium, Alzheimer's Disease and mild cognitive impairment (Giattino et al., 2017). Beta waves (13-30 Hz) are related to behavior and actions. These waves are located around cortical activity, seen in both sides of the frontal and parietal lobes but are most predominant in the frontal region. Beta waves are associated with thinking and assessing (Kumar & Bhuvaneswari, 2012). They tend to occur in conscious states like talking, problem solving, judgement, and decision making. Delta waves are the slowest waves (0.1-4 Hz) but have the highest amplitude. They are typically seen in all stages of sleep, especially stage 3 and 4 and are considered abnormal in adults who are awake. Theta waves range from 4-8 Hz and are typically present during deep relaxation and meditation. They are considered abnormal in adults but are normal under 13 years. Gamma waves fall around 30-100 Hz and require digital EEG techniques to for proper measurement. These waves occur during hyper-alertness and integration of sensory input. Gamma properly combines senses and memory experiences together (Kumar & Bhuvaneswari, 2012).

EEG changes associated with delirium

Combining the pioneering work of Caton (1875) and Romano and Engel (1944) with research conducted by Jacobson, Leuchter, & Walter (Jacobson et al., 1993) resulted in the acceptance that an increase in slow EEG activity (delta, theta) and a diminution of the occipital alpha rhythm characterize a delirium (Reischies et al., 2005). Early work attempting to associate waveform patterns found significant differences in the EEG spectra between delirious patients and healthy controls (Koponen et al., 1989). Specifically, they found a reduction in the proportion of alpha activity and mean frequency were associated with declining cognitive status based on clinical assessment using the Mini-Mental Status Exam (MMSE). When attempting to distinguish delirium for "normal" cases, researchers found use of relative alpha power captured 96% of delirium and an association between proportions between delta activity and length of delirium and hospital stay. When separated into delirious and non-delirious groups, EEG results showed a significant difference ($p < 0.001$)(Trzepacz et al., 1988). Similar to prior studies using conventional EEG analysis, an association between spectral EEG changes and severity of cognitive deterioration in delirium. A correlation between delta wave percentage and mean frequency has also been correlated with lengths of delirium and hospitalization (Koponen et al., 1989). Analysis of EEG power spectra comparing ICU patients on the same sedation medication regimen revealed significant differences in mean values for the delirium-negative patients which were 55.6%, 29.5% and 14.9% for the theta, alpha and beta frequencies, respectively, and for the delirium-positive patients, 69.0%, 21.0%, and 10%, respectively (Plaschke et al., 2007). The post-hoc analysis revealed significantly higher power for the theta band ($p = 0.008$). A three-way interaction analysis looking at, delirium x frequency band x electrode site ($p = 0.033$) confirmed a reduction in fast and an increase in slower frequencies. Specifically, higher relative theta power

and reduced alpha power for the delirium group compared to non-delirious patients at all 16 electrode sites and reduced beta power at frontocentral sites for the delirium group was observed. To emphasize the direction of the EEG changes, the alpha/theta ratio was calculated. The average ratio from all 16 electrodes values was 0.296 for the delirium group and 0.548 for the non-delirium group (p = 0.039). When comparing the EEG differences between those with delirium only, those with dementia only and those with co-existing delirium and dementia, there are consistently greater abnormalities (Jacobson et al., 1993). Evaluating theta activity and relative power of delta frequency bands and brain rate mapping (absolute power with scale maximum of 103 microvolts squared) resulted in accurate discrimination between delirium and dementia 90-95% of the time. The culmination of work has shown consistent and recognizable electrophysiological abnormalities with the presence of delirium readily detected by EEG, particularly when combined with quantitative analysis.

Advances in EEG related to detecting changes

Over the last 15 or so years, studies have attempted to identify which EEG leads and potential methods of signal processing analysis of the waveforms were needed to discriminate delirium from non-delirium (Numan, 2017). As the science related to EEG increased, a focus became reducing the number of leads required for monitoring. Therefore, researchers began to investigate which leads (or location of leads) were needed to detect various pathological states. Additionally, scientists have begun to develop algorithms to process the EEG data and, therefore, detect meaningful changes consistent with specific conditions and disease states, including delirium. This has since led to a reduction in the number of leads required to monitor some conditions, such as level of awareness and wakefulness. Using this newer technology, limited

leads with machine processed EEG may provide a viable option for routine EEG monitoring by reducing the burden and need for expert interpretation.

van der Kooi (2015) used a bipolar-electrode derivation to determine EEG characteristics, showing large differences between patients with and without delirium while also discriminating delirium from other causes to reduce the number of required EEG leads. In that study, and re-affirmed in a subsequent study, they determined that two leads, attached on the forehead between the center of the head and ear, distinguished delirium from non-delirium (van der Kooi et al., 2015).

Following on the success of several other studies using a variety of modified two-electrode devices, researchers have confirmed identification of EEG changes consistent with delirium. Numan (2017) conducted a study to determine if Ag/AgCl electrodes applied to the head using a headband would provide the data needed to determine delirium status. Bipolar recordings from an international 10-20 EEG system were used to obtain EEG data using three derivations (Numan, 2017).

Based on a dichotomous classification by delirium experts - delirium and probably delirious - they examined several cut-off points of the relative delta power. Using a relative delta power of 1-4 Hz, they found fair accuracy (AUC=0.75) when attempting to discriminate delirium from probably delirium. When the relative delta range was widened to 1-6 Hz, accuracy improved slightly (AUC=.78). Although they deviated from the perfect discriminating test (AUC=1.00), these results were significantly better than chance (AUC=0.50). In the proof-of-concept study, accuracy of the relative delta power to discriminate between definitely delirious patients and definitely non-delirious patients was significantly higher (AUC = 0.99).

Monitoring patients at risk for delirium in clinical practice is more feasible using a bipolar derivation as compared to full EEG (van der Kooi et al., 2015). Researchers have also discovered alterations in relative delta power capable of delirium detection using a bipolar derivation. Unlike previous studies that evaluated results based on relative powers over all EEG channels, researchers have determined the discriminative accuracy of the EEG features was high, with high importance values for relative delta, alpha and beta power to distinguish between hypoactive delirium and controls. Distinction between patients with hypoactive delirium patients and those who are sedated was mainly based on betweenness centrality in the alpha frequency band. While full EEG is not practical on all patients in routine daily practice, functional network measures have been found to contribute to the distinction between hypoactive delirium and recovery from anesthesia. These findings suggest that these conditions can be distinguished with EEG (van der Kooi et al., 2015).

Further research may help determine device usefulness for selecting appropriate prevention and treatment strategies to decrease morbidity and mortality, improve patient outcomes, and reduce cost of care. Future studies may potentially eliminate the need for frequent intermittent nurse delirium assessments by providing an objective method to ascertain which nurse-driven interventions are most effective in preventing and treating delirium. To improve recognition above the current state, a new diagnostic tool for the purpose of identifying developing delirium should increase sensitivity to greater than 50%. If processed EEG data accurately identifies delirium in critically ill patients, this would potentially allow for assessment of the 58% of patients currently not accurately identified.

Conclusion

It has been known for decades background EEG slowing occurs during delirium (Mulkey, Hardin, Olson, et al., 2018). Use of routine full EEG monitoring for daily delirium screening is time-consuming and impractical because these studies can only be performed and interpreted by specifically trained personnel. Because EEG monitoring with automatic processing has become technically feasible, detection protocols with a limited number of electrodes and automatic processing could increase recognition of delirium (Mulkey, Hardin, Olson, et al., 2018). Recent studies using a 2-electrode EEG system showed significant differences between patients with and without delirium. Although cognitive testing has been the historic gold standard for the identification of delirium, if EEG-based detection shows usefulness, this approach may better fit the need for objective evaluation of patients, which is less dependent on observer interpretation of patient response (Dries, 2018). However, the EEG technique for detection must be validated.

Delirium is an acute disorder of attention and global cognitive function characterized by fluctuating symptoms. Many of those who survive an episode delirium will be left with persistent cognitive impairment. There are no effective and scalable recovery models to remediate ICU-acquired cognitive impairment. The routine use of early delirium identification and preventive measures in the ICU is widely endorsed given the high prevalence of delirium, its deleterious effects on patient outcome, and the high costs related to these effects. The routine use of a physiologic method for delirium detection may facilitate early recognition in those patients at greatest risk at a point when interventions are more likely to be effective.

Earlier detection of delirium in the older adult ICU patient population may facilitate use of early preventive strategies, but a physiologic objective method for delirium detection is

unclear. The biochemical pathways for attention and cognition are still being characterized. Based on the prior work and the pathophysiologic mechanisms described above, evaluating the use of physiologic methods for early detection represents a major step forward in the field of delirium. Unfortunately, a limited number of studies have evaluated these devices for analyzing EEG waveform analysis to detect delirium.

<div align="center">Application to nursing</div>

Delirium is complex, may be subtle, and is highly under-diagnosed (Kluger et al., 2018). Despite our best efforts to prevent delirium, it inevitably strikes the vast majority of our patients. Currently, nurses do not have the necessary equipment at the bedside to provide early identification of delirium. Earlier detection, when nursing interventions would be more effective, could likely reduce the long-term ramifications.

Having an objective method nurses can easily use, could change the standard of care by providing earlier identification. Physiologic monitoring may also provide identification prior to symptom onset, especially in the setting of hypoactive delirium, allowing for the greatest impact on patient outcomes. Because a physiologic monitor is lacking, nurses are hampered in providing optimal patient care and conducting research on this pervasive problem.

Until such a time when physiologic monitoring is available, nurses need to understand the pathophysiology of delirium so they can identify patients at increased risk of delirium. Because prevention and early identification are key to improving patient outcomes, nurses should remain proficient in the use of bedside clinical assessment tools such as the CAM-ICU. Most importantly, it is critical that nurses continue to be strong patient advocates by providing high quality basic nursing care because this is the best method of delirium prevention and treatment.

CHAPTER FIVE: IS LIMITED-LEAD EEG AN OPTION FOR DELIRIUM MONITORING? MANUSCRIPT

Introduction

Delirium is a serious acute condition that causes fluctuating disturbances in cognition, awareness and attention and triples mortality in those affected (Mulkey, Hardin, Olson, et al., 2018). In hospitalized older adults, delirium is the most common neuropsychiatric condition, affecting as many as 80% in the intensive care unit (ICU) (Mulkey, Roberson, et al., 2018). More than 58% of ICU patients cannot be assessed using currently available screening tools, such as the Confusion Assessment Method-ICU (CAM-ICU) and the ICU Delirium Screening Checklist (ICDSC) (Mulkey, Roberson, et al., 2018). Of those screened, clinicians only detect about 40% of delirium cases. This is likely due to the need for initial and ongoing training to maintain screening accuracy and the tendency to dismiss positive screens as due to dementia or another cause (M. A. Mulkey, Hardin, S.R., Olson, D.M., Munro, C.L., Everhart, D.E., 2019). Therefore, an objective physiologic monitor capable of early accurate detection is desperately needed.

Electroencephalogram (EEG) was identified decades ago as the true gold standard for delirium detection but its use has not been feasible due to limited resources (M. A. Mulkey, D. E. Everhart, S. Kim, et al., 2019; Obrecht et al., 1979; Romano & Engel, 1944). When patients are experiencing delirium, the EEG shows generalized slowing of background activity, slowing of awake waves (alpha waves) with significant decreases in power, increases in sleep waves (theta waves) and deep sleep waves (delta waves) power, and sleep wave intrusion (van der Kooi, 2015; van der Kooi, Slooter, et al., 2014). As a result, ratios of sleep waves to awake waves (theta waves to alpha waves and delta waves to alpha waves) are significantly higher (van der Kooi, 2015; van der Kooi, Slooter, et al., 2014). Prior research has shown that these EEG

characteristics distinguish delirium from non-delirious states. Additionally, EEG allows discrimination between delirium and other etiologies associated with behavioral changes, such as sedation and dementia (van der Kooi, 2015; van der Kooi, Slooter, et al., 2014).

Over the last couple of decades, with advances in technology, available limited lead EEG devices have become 'nurse friendly'(M. A Mulkey et al., 2019). Methods of analyses have been developed that maximize signal concentration and filter frequencies to smooth variations (Zhou et al., 2008). This process 'cleans the EEG waveform' by removing interference from other equipment such as ECG monitors and current from electronic beds. Programs using these advanced methods can provide automatic processing capable of detecting the known changes in EEG waveform. As a result, limited lead EEG devices capable of processing may provide a more practical, feasible option for nurses. Additionally, earlier detection, even prior to behavioral symptom onset, may be possible (Mulkey, Hardin, & Schoemann, 2018; Tao et al., 2019). Therefore, the hypothesis that drove this study was that the Ceribell EEG monitoring device could provide a physiologic method for early and possibly predictive delirium identification (M. A Mulkey et al., 2019).

Methods

Setting and Sample

This pilot exploratory proof of concept study used a prospective design to build on prior research. After receiving Institutional Review Board approval, research was conducted at a tertiary academic medical center in eastern North Carolina. The study was designed to evaluate signal-processed EEG waveform patterns obtained from a commercially available device, the Ceribell. Differences in EEG waveforms were evaluated based on delirium status determined by investigator-performed CAM-ICU assessments while patients received routine clinical care.

A total of 17 critically ill older adults (age >50 years) meeting criteria were enrolled between March 2019 and March 2020. Primary diagnoses were Motor Vehicle Collision, Respiratory failure/Pneumonia, congestive heart failure (CHF), ST segment elevation myocardial infarction (STEMI), gastrointestinal (GI) bleed, abdominal mass and bowel perforation. Prior to enrollment, informed consent was obtained from the subject (n=1) or their legally authorized representative (n=16). To maximize the likelihood of capturing EEG data from delirium positive participants, recruitment was restricted to older adults requiring mechanical ventilation who were able to participate in a CAM-ICU assessment. Because the investigator only spoke English, patients unable to speak and understand English were excluded.

Measures

The methods have been previously described in full in M. A Mulkey et al. (2019). In brief, hand-held EEG monitors (Ceribell Inc.) were placed on subjects by the primary investigator. Continuous EEG (cEEG) data were then recorded for 2-hours for each of 4 consecutive days from each consented participant while in the intensive care unit (ICU). Delirium assessments using CAM-ICU were obtained daily after the first hour of cEEG. Demographics and past medical history were obtained from the data available from the electronic medical record during abstracting, prior to discharge.

Electroencephalography (EEG)

Raw EEG data includes both brainwave and electrical activities from the heart, eyes, electronic devices such as beds and telemetry monitoring, and EEG electrode motion interference called "ambient noise" or artifact. Prior to analysis of the EEG data, those noise components must be filtered out of each channel using traditional high- and low-pass filters and advanced independent component analysis filters. Then, raw EEG signals from each channel can

be subjected to power spectral density analysis to determine relative presence of 'high' and 'low' frequency components. By means of computational algorithms, EEG characteristics can be documented in an objective and quantitative way. Quantitative EEG (qEEG) relies on extensive technical knowledge in the field of digital signal processing and offers a wider spectrum of possible applications to analyze the data. Therefore, study data were evaluated using this method, known as spectral density analysis (Shinozaki et al., 2018).

Electrophysiologic signals characteristic of delirium are often reported as 'diffuse slowing,' meaning that the brain waves are of a reduced frequency. Therefore, the emergence of low-frequency waves indicates potential occurrence of delirium in the raw EEG. The fact that all EEG channels can detect the same reduction in frequency suggests that use of a small number of channels would be sufficient to obtain relevant data indicative of delirium.

Ceribell derived EEG utilizes 10 electrodes as opposed to traditional EEG that typically uses 21 electrodes. These 10 electrodes, that may be easily applied by non-experts such as nurses, produces 8 channels of EEG data. Raw EEG data were recorded on the Ceribell device and uploaded to a cloud server. These data were then downloaded and parsed in preparation for analysis in MATLAB. Using MATLAB, spectral density and independent analyses were combined with appropriate investigator developed mathematical algorithms to analyze EEG signals. Using ratios to reflect the relative presence of high- and low-frequency activity, EEG data are ready to be evaluated for the presence of delirium. Due to the objective nature of EEG, interrater reliability concerns seen with currently available bedside screening tools are ruled out as confounders. EEG can be strongly correlated with patient outcomes and may provide additional information for goals of care decisions (Shinozaki et al., 2019; Shinozaki et al., 2018). As a result, screening is practical, feasible and greatly facilitated.

Statistical analysis

Descriptive statistics were used to summarize subject demographic and clinical characteristics. Summary and exploratory statistics were performed using SPSS (version 26) statistical analysis (IBM Corporation, 2016). Frequencies and percentages were used to describe demographic data obtained including age, gender, and race. Demographics were analyzed to determine if patient sampling was representative of currently available ICU delirium literature. Specifically, hospital and ICU length of stay (LOS) and discharge disposition were examined. Data from 17 subjects were then analyzed to explore associations between the Ceribell-derived theta/alpha ratio, delta/alpha ratios and clinical delirium.

Researcher determined delirium status based on CAM-ICU assessments were dichotomized as delirium present and delirium not present and compared with dependent variables from signal processed EEG including delta to alpha and theta to alpha ratios as continuous variables. Subject characteristics were tested for normalcy using the Kolmogorov-Smirnov test. Continuous variables were not normally distributed and therefore the Kruskal-Wallis test was utilized for group comparisons (Charlson et al., 1987; Knaus et al., 1991; Marshall et al., 1995).

Results

Demographics

A total of 17 participants from 3 ICUs (Medical, Surgical and Cardiac) were included in the analysis. One subject without delirium did not have a 1-minute epoch of artifact free data and was excluded from exploratory analysis of EEG ratios. Mean age for all subjects was 66.69 (SD 8.731). Nine subjects (53%) were male, 65% were Caucasian. Subjects were similar in that 86% were living at home prior to hospitalization. Overall hospital LOS was 24.80 days (SD 12.80)

with an ICU LOS of 17.80 days (SD 12.47). The average number of ventilator days was 12.53

days (SD 12.73).

While severity of illness scores such as Acute Physiologic Assessment and Chronic Health

Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) were not available,

mean Charlson Co-morbidity Index Scores, a 6-point weighted index used to predict risk of

death within one year of hospitalization and higher resource use, was calculated at 3.73 (SD

3.052). These Index scores indicate a five-year survival rate of less than 28% (Charlson et al.,

1987). Of the 38 observations, 9 subjects (52.94%) were positive for delirium during the

enrollment period. See Table 1and 2 for additional demographics.

Table 6. Participant demographics

Variables	N=17	
Delirium Status		
Positive	9	53%
Negative	8	
Gender		
Male	9	53%
Female	8	
Age		
50-59	5	31%
60-69	5	31%
70-79	6	38%
80-89	1	6%
Marital Status		
Single- never married	2	12%
Married –live together	9	53%
Married- live apart	1	6%
Divorced	2	12%
Widowed	3	12%
Race		
Caucasian	11	65%
African-American	6	
Living Situation		
Home	15	88%
Institution	2	
Smoking status		
Smoker	6	35%
Never Smoked	4	24%
Ex-smoker	7	41%
Alcohol Use		
Yes	6	35%
No	11	
Medications currently receiving		
Anti-hypertensive	6	43%
Peptic Ulcer Prophylaxis	4	29%
Benzodiazepine	1	7%
Anti-depressant	2	86%
Psychoactive	1	7%

Insurance
Commercial	2	11%
Medicaid	4	24%
Medicare	9	53%
Self-pay	1	6%
VA	1	6%

Discharge Disposition
Home	4	24%
Skilled Nursing	3	12%
Long-term Care	7	41%
Expired	3	12%

Table 7. Participant demographics by Delirium Status

Variables N=17	Delirium positive (n=9)		Delirium negative (n=8)	
Male	7	78%	2	25%
Female	2	22%	6	75 %
Age				
50-59	2	22%	3	38%
60-69	2	22%	3	38%
70-79	5	56%	1	13%
80-89	0		1	13%
Marital Status				
Single- never married	1	11%	1	13%
Married –live together	4	44%	5	63%
Married- live apart	1	11%	0	
Divorced	1		1	13%
Widowed	2		1	13%
Race				
Caucasian	6		5	63%
African-American	3		3	38%
Living Situation				
Home	7		8	100%
Institution	2		0	
Smoking status				
Smoker	3		3	38%
Never Smoked	1		3	38%
Ex-smoker	4		3	38%
Alcohol Use				
Yes	4		2	
No	5		6	
Medications currently receiving				
Anti-hypertensive	3		3	
Peptic Ulcer Prophylaxis	1		3	
Benzodiazepine	0		1	
Anti-depressant	0		2	
Psychoactive	1		0	
Insurance				
VA	1		0	
Commercial	1		1	
Medicaid	2		2	

|		
Medicare	5	4
Self-pay	0	1
Discharge Disposition		
Home	1	3
Skilled Nursing	1	2
Long-term Care	3	4
Expired	2	1
Hospital LOS	23.0 (9-54)	25.67 (11-41)
ICU LOS	14.88 (5-43)	19.33 (5-41)
Delta/Alpha Ratio	2.52428 (1.4788 -3.5678)	2.21714 (1.3004-3.2802)
Theta/Alpha Ratio	1.5661 (1.1867-2.0822)	1.4024 (1.2604-1.6195)

Association between EEG and clinical delirium

To fully examine these data, a model was created in which an average of all subject positive or negative results was used (n=16), meaning each subject had one delta/alpha and one theta/alpha ratio reflecting an average of all ratios obtained during enrollment. Average delta/alpha ratios across all subjects were 2.4378 (SD 0.73650) while theta/alpha ratios were 1.5262 (SD 0.2795). Subjects identified as delirium positive had a mean delta/theta ratio of 2.5243 (SD 0.7450) while those who were delirium negative had a ratio of 2.2171 (SD 0.7214). Theta/alpha ratios were 1.5661 (SD0.7451) for delirium negative and 1.5661 (SD 0.3100) and 1.4024 (SD0.1152) for delirium positive subjects. Mann-Whitney U test revealed no significant difference in sleep/wake ratios of delirious versus non-delirious subjects. Delta/alpha ratios were Md=2.1345, n=6 while delirious subjects were 2.5795, n=10, U= 38.50, z=.923, p=.36, r=.033 Theta/alpha ratios were Md=1.3862, n=6 while delirious subjects were 1.5618, n=10, U=40.00, z=1.085, p=.28, r=.127. However, effect sizes were small to moderate for delta/alpha ratios and large for theta/alpha ratios. Kruskal-Wallis revealed there was no statistically significant difference in ratios between those with and without delirium, X^2 (2, n=16) = 2.356, p=0.308. After controlling for the patient as a random effect (repeated) the delta/alpha ratios were b = -.99, p = 0.77 and theta/alpha ratios were b = 1.70, p = 0.09, therefore, not a statistically significant predictor of delirium. Although sleep/wake ratios were not statistically significant, delta/theta ratios were significant b = 1.52, p = 0.0487.

Distribution of D2A_Daily_Ave

F	0.95
Prob > F	0.3361
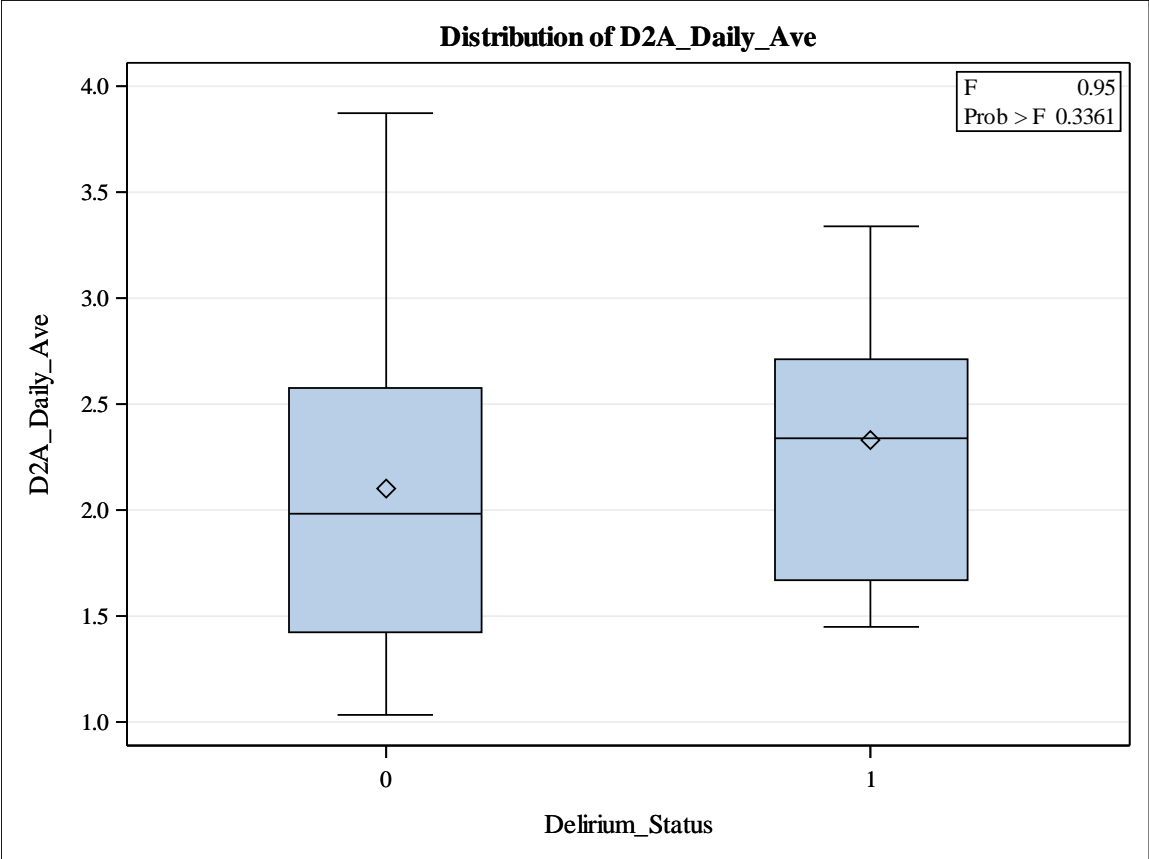
Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	0.51853364	0.51853364	0.95	0.3361
Error	36	19.63785731	0.54549604		
Corrected Total	37	20.15639094			

Figure 8. Delta/Alpha Ratio Daily Average
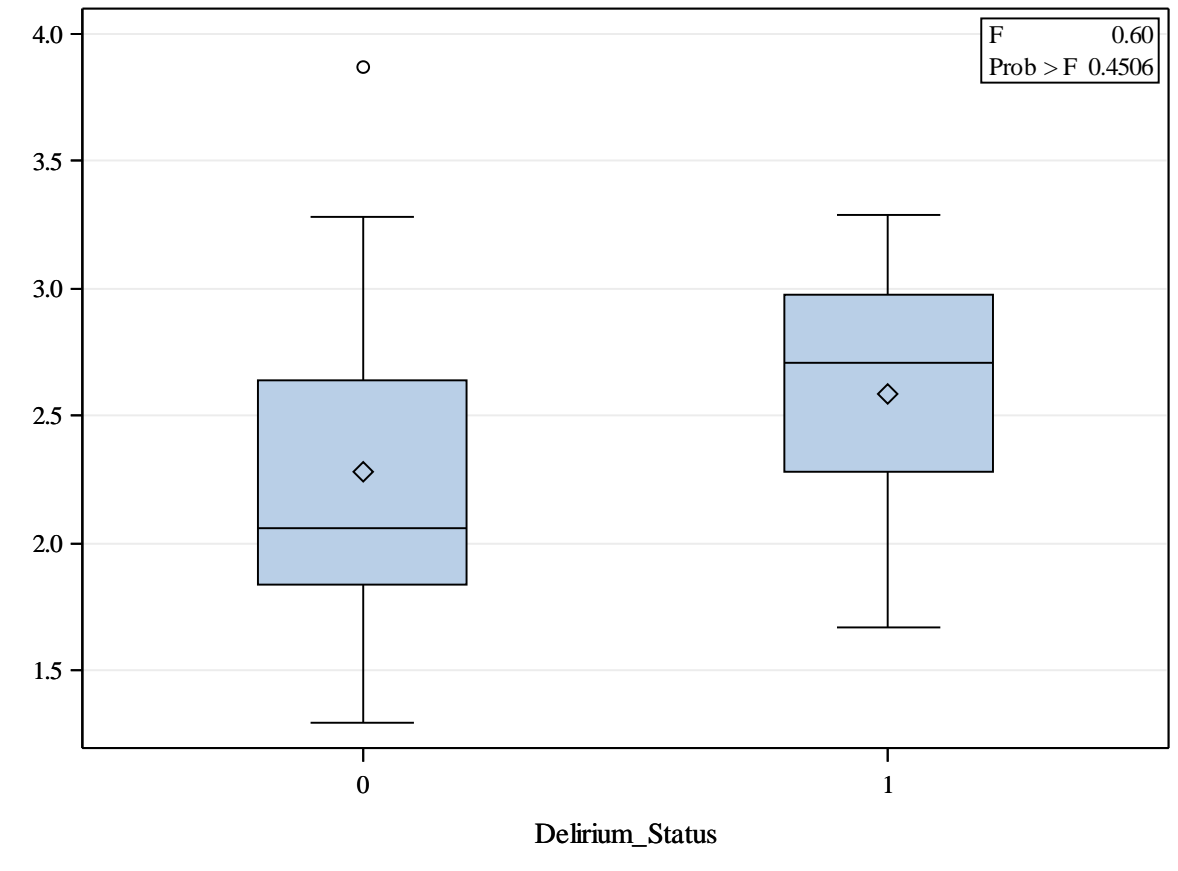
Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	0.32531552	0.32531552	0.60	0.4506
Error	14	7.56066634	0.54004760		
Corrected Total	15	7.88598185			

Figure 9.Delta/Alpha Ratio using only the 1st observation

Distribution of T2A_Daily_Ave
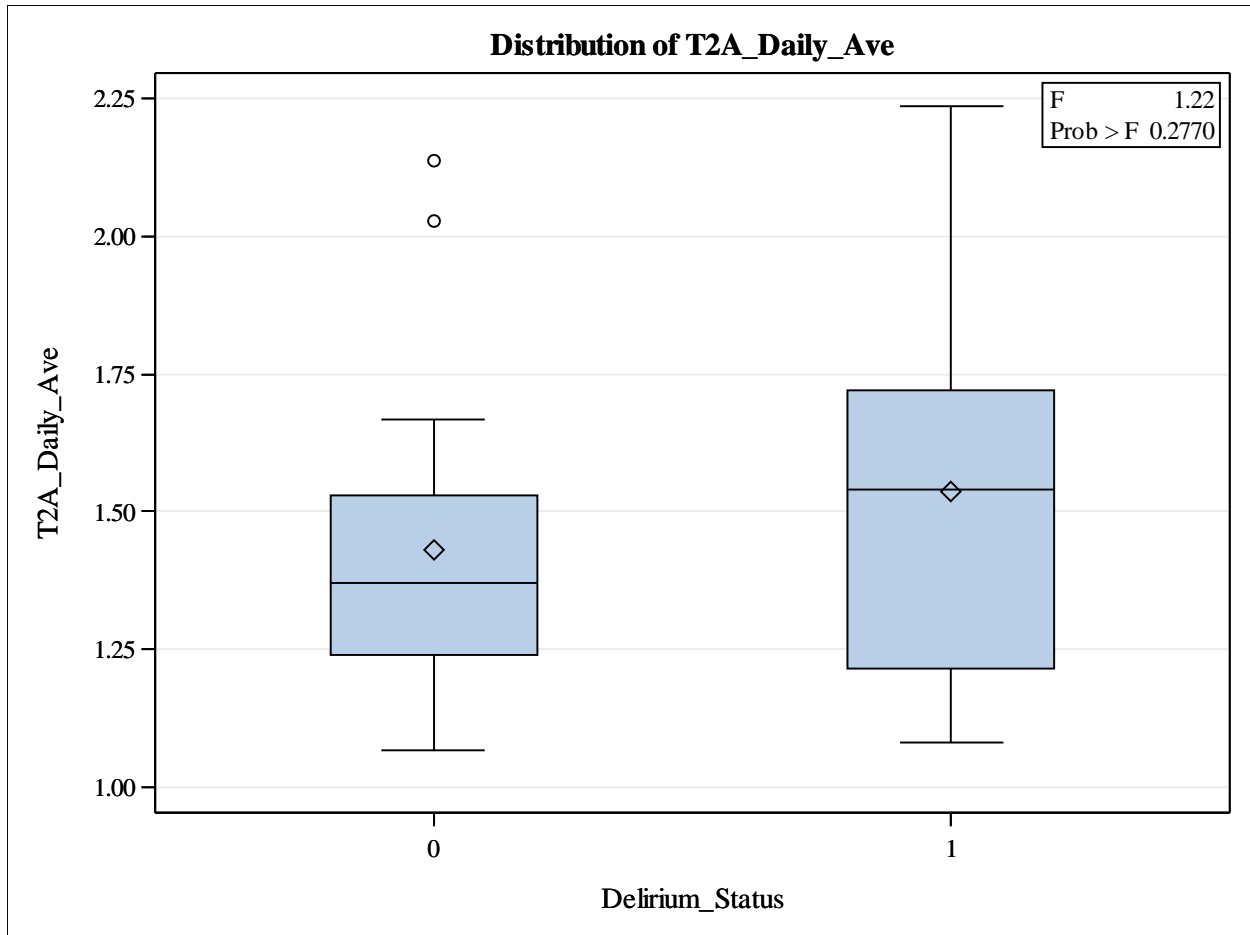
Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	0.10853414	0.10853414	1.22	0.2770
Error	36	3.20707184	0.08908533		
Corrected Total	37	3.31560598			

Figure 10. Theta/Alpha Ratio Daily Average
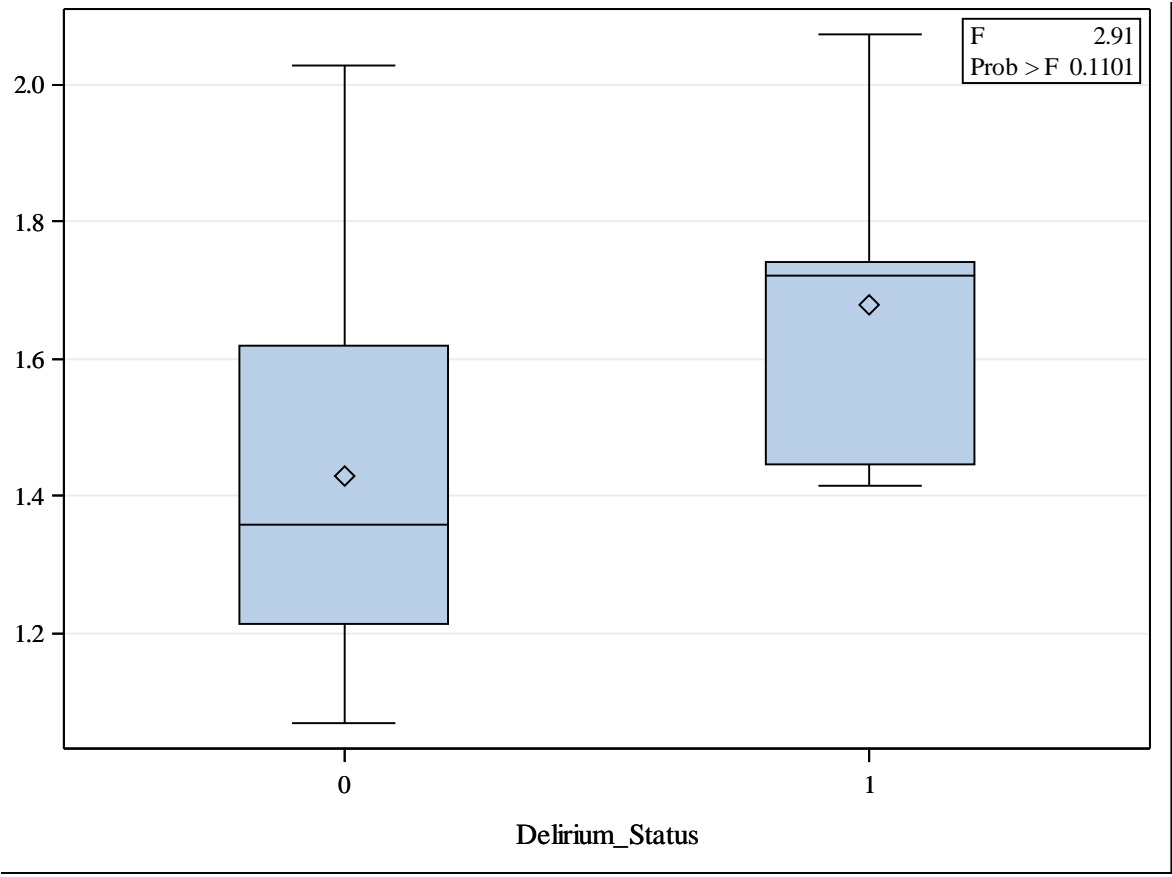
Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	0.21469897	0.21469897	2.91	0.1101
Error	14	1.03318039	0.07379860		
Corrected Total	15	1.24787936			

Figure 11. Theta/Alpha Ratio Using only the 1st observation

Distribution of D2T_Daily_Ave

F	0.97
Prob > F	0.3312
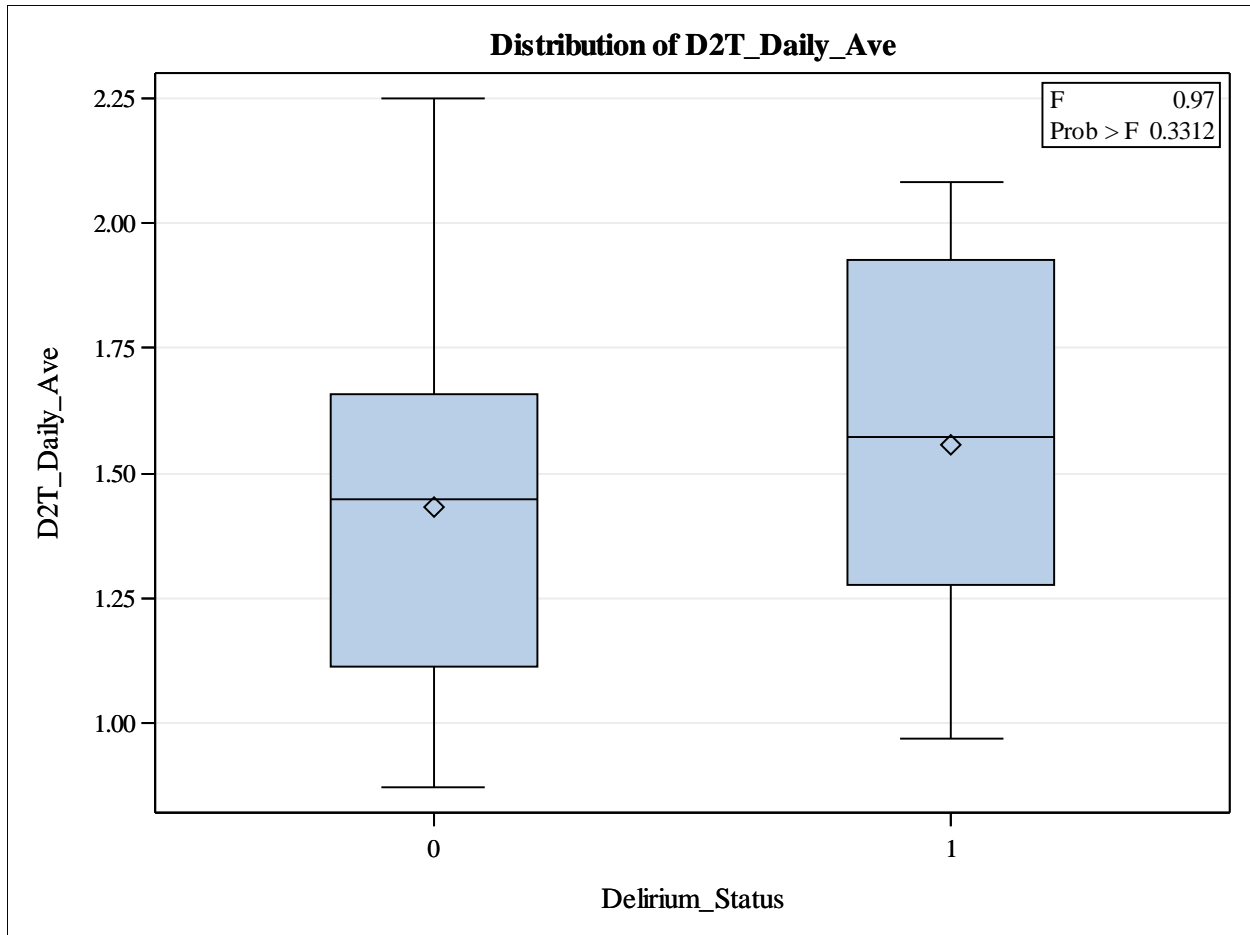
Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	0.15107926	0.15107926	0.97	0.3312
Error	36	5.60578776	0.15571633		
Corrected Total	37	5.75686702			

Figure 12. Delta/Theta Ratio Daily Average

| | | | F | 0.01 |
| | | | Prob > F | 0.9199 |
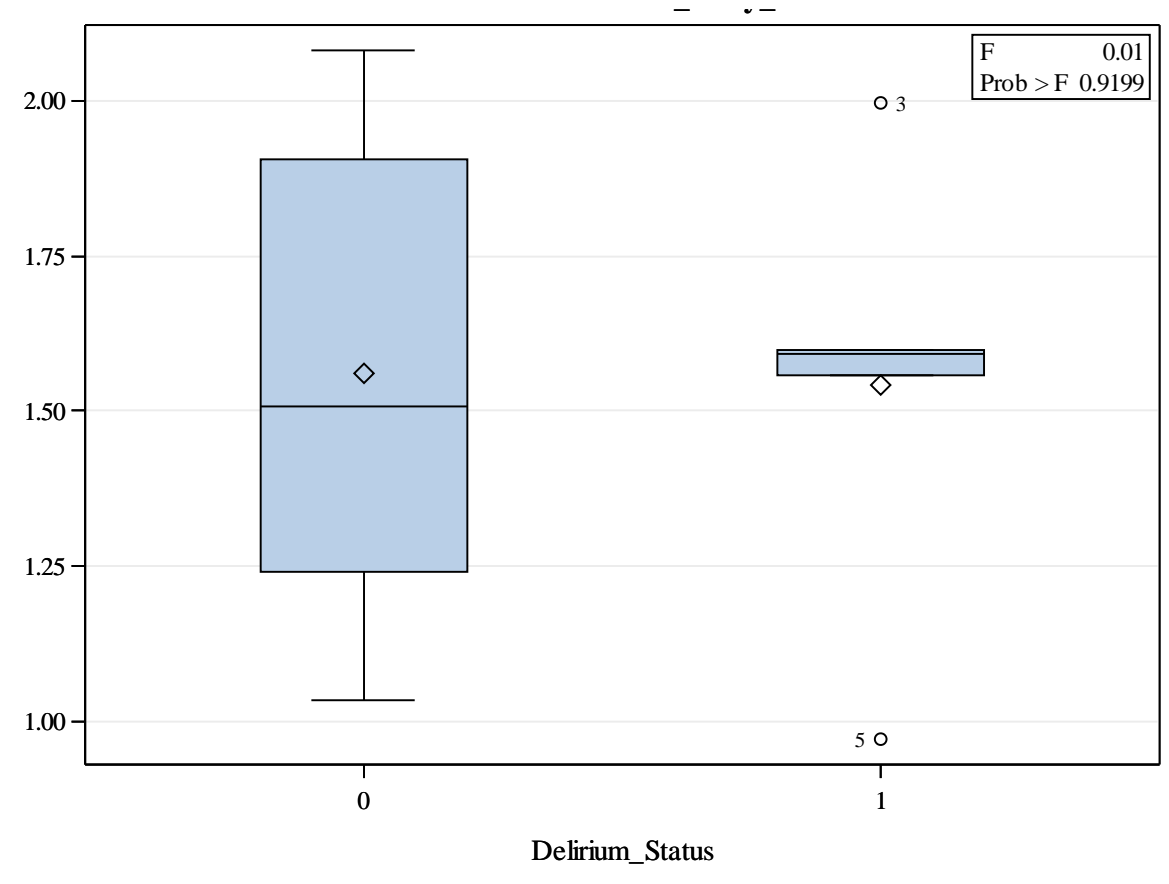
Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	0.00129270	0.00129270	0.01	0.9199
Error	14	1.72615212	0.12329658		
Corrected Total	15	1.72744481			

Figure 13. Delta/Theta Ratios Using only the first observation (Day One of Enrollment period)

Discussion

Key findings and interpretation

While the data presented here did not show that sleep/wake ratios were associated with the clinical presence of delirium, it is likely this study was underpowered to detect statistically significant differences between those with delirium compared to those for whom delirium was not detected. However, even with the small sample size and controlling for random effects, the

trend in p-values was approaching statistical significance. Being underpowered to detect statistically significant differences may explain why our study findings are not consistent with prior research. Although van der Kooi (2015) (n= 28) and Plaschke et al. (2007) (n=37) found statistical significance with small samples, there were more total subjects and, therefore, more delirium positive cases. Despite the lack of statistical significance, interestingly, all ratios were higher in delirium patients than non-delirium patients. Having some overlap in ranges between those identified as delirium positive compared to those who were delirium negative may also partially explain some of the reason why the null hypothesis cannot be rejected in this sample.

The search for EEG-based delirium biomarkers has a long history. Prior studies have suggested a distinguishable marked difference in delirium compared to normal awareness. Since the 1940s, reports of patterns in EEG data while using only 2 channels have indicated that identification of delirium is possible. However, currently available technologies using a small number of EEG leads are not "tuned" for delirium screening and lack a form factor appropriate for mass screening. Nevertheless, only recently has application of computational algorithms and use of spectral density analysis demonstrated that delirium may be detected using a limited number of leads. Studies have confirmed that the sensitivity and specificity of limited EEG leads are excellent and comparable to those from machines with the traditional 21 leads for this purpose (Plaschke et al., 2007; van der Kooi, 2015; van der Kooi et al., 2012b). Previous literature supports the notion that EEG is useful for detecting delirium. However, the capacity for using a point-of-care EEG device such as Ceribell has not been determined. Studies attempting to identify biomarkers of delirium, such as our study, are limited to small numbers of participants. Therefore, association of findings from this type of screening method have not been

established with patient outcomes such as hospital LOS, discharge disposition, and mortality or the effect of intervention on these outcomes.

This study is the first to use the Ceribell point-of-care EEG device to demonstrate an association between EEG signal biomarkers and their association with delirium and patient outcomes. Despite the lack of statistical significance demonstrated by our data, the potential usefulness of Ceribell derived EEG data to identify patients at risk for delirium and predict patient outcomes such as hospital LOS, discharge disposition, and mortality among older hospitalized patients cannot be ruled out. With additional clinical validation studies using larger sample sizes, Ceribell-derived EEG biomarkers, such as those used in this study, may still be an option for enabling early intervention and potentially improve the care of patients at risk of delirium.

Delirium is particularly dangerous because the ability to recognize and manage delirium early is lacking. The simple, noninvasive objective nature of limited lead EEG makes it ideal for routine delirium screening when used in appropriate populations with the potential to be fast and easy, similar to measuring vital signs. A positive result would provide an early alarm to trigger a more comprehensive workup for an acute illness. Therefore, limited lead EEG may be more clinically relevant than realized. In the future, EEG may also potentially provide an objective and quantitative replacement for "altered mental status" in prognostic models such as the Sequential Organ Failure Assessment (SOFA). As the aging population continues to expand rapidly, efficient modalities for delirium screening such as Ceribell-derived EEG are predicted to be in high demand.

Limitations

The usefulness of limited lead EEG for delirium screening is predicated on the assumption that EEG changes are generalized or diffuse. Therefore, focal changes, such as seizure activity or a structural brain abnormality may confound results. Limitations of this study include the small sample size, enrollment of participants from a single institution in the Southeast region of the United States as well as use of a daily average from all 8 channels for each observation. Thus, potential generalizability would need to be tested in the future with a larger sample size using a multicenter approach. Nevertheless, while not statistically significant, we have shown that the Ceribell-derived EEG is capable of detecting changes in EEG presumed to differentiate delirium from a non-delirious state. These results encourage further exploration of Ceribell derived EEG data to better understand delirium's impact on neuroelectrical changes and ways to prevent, manage, and treat it in the hopes of potentially improving patient outcomes.

Conclusion

While being under powered minimized opportunities to detect statistical differences in EEG derived ratios using spectral density analysis, EEG ratios tended to be higher in patients with delirium with sleep wake ratios trending toward significance and delta/theta ratios were statistically significant. Determining whether point-of-care limited lead EEG may be able to predict adverse patient outcomes in an older critically ill population remains largely unknown. Importantly, although this population is at highest risk for mortality, delirium cannot be easily identified by current clinical assessments. Therefore, further investigation of limited lead EEG for delirium detection is warranted.

Delirium is a serious acute condition that causes fluctuating disturbances in cognition, awareness and attention and triples mortality in those affected (Mulkey, Hardin, Olson, et al., 2018). In hospitalized older adults, delirium is the most common neuropsychiatric condition,

affecting as many as 80% in the intensive care unit (ICU) (Mulkey, Roberson, et al., 2018).

More than 58% of ICU patients cannot be assessed using currently available screening tools,

such as the Confusion Assessment Method-ICU (CAM-ICU) and the ICU Delirium Screening

Checklist (ICDSC) (Mulkey, Roberson, et al., 2018). Of those screened, clinicians only detect

about 40% of delirium cases. This is likely due to the need for initial and ongoing training to

maintain screening accuracy and the tendency to dismiss positive screens as due to dementia or

another cause (M. A. Mulkey, Hardin, S.R., Olson, D.M., Munro, C.L., Everhart, D.E., 2019).

Therefore, an objective physiologic monitor capable of early accurate detection is desperately

needed.

Electroencephalogram (EEG) was identified decades ago as the true gold standard for

delirium detection but its use has not been feasible due to limited resources (M. A. Mulkey, D.

E. Everhart, S. Kim, et al., 2019; Obrecht et al., 1979; Romano & Engel, 1944). When patients

are experiencing delirium, the EEG shows generalized slowing of background activity, slowing

of awake waves (alpha waves) with significant decreases in power, increases in sleep waves

(theta waves) and deep sleep waves (delta waves) power, and sleep wave intrusion (van der

Kooi, 2015; van der Kooi, Slooter, et al., 2014). As a result, ratios of sleep waves to awake

waves (theta waves to alpha waves and delta waves to alpha waves) are significantly higher (van

der Kooi, 2015; van der Kooi, Slooter, et al., 2014). Prior research has shown that these EEG

characteristics distinguish delirium from non-delirious states. Additionally, EEG allows

discrimination between delirium and other etiologies associated with behavioral changes, such as

sedation and dementia (van der Kooi, 2015; van der Kooi, Slooter, et al., 2014).

Over the last couple of decades, with advances in technology, available limited lead EEG

devices have become 'nurse friendly.'(M. A Mulkey et al., 2019) Methods of analyses have

been developed that maximize signal concentration and filter frequencies to smooth variations

(Zhou et al., 2008). This process 'cleans the EEG waveform' by removing interference from

other equipment such as ECG monitors and current from electronic beds. Programs using these

advanced methods can provide automatic processing capable of detecting the known changes in

EEG waveform. As a result, limited lead EEG devices capable of processing may provide a more

practical, feasible option for nurses. Additionally, earlier detection, even prior to behavioral

symptom onset, may be possible (Mulkey, Hardin, & Schoemann, 2018; Tao et al., 2019).

Therefore, the hypothesis that drove this study was that the Ceribell EEG monitoring device

could provide a physiologic method for early and possibly predictive delirium identification (M.

A Mulkey et al., 2019).

Methods

Setting and Sample

This pilot exploratory proof of concept study used a prospective design to build on prior

research. After receiving Institutional review board approval, research was conducted at a

tertiary academic medical center in eastern North Carolina. The study was designed to evaluate

signal-processed EEG waveform patterns obtained from a commercially available device, the

Ceribell. Differences in EEG waveforms were evaluated based on delirium status determined by

investigator-performed CAM-ICU assessments while patients received routine clinical care.

A total of 17 critically ill older adults (age >50 years) meeting criteria were enrolled

between March 2019 to March 2020. Primary diagnoses were Motor Vehicle Collision,

Respiratory failure/Pneumonia, CHF, ST elevation MI, GI bleed, abdominal mass and bowel

perforation. Prior to enrollment, informed consent was obtained from the patient (n=1) or their

legally authorized representative (n=16). To maximize the likelihood of capturing EEG data

from delirium positive participants, recruitment was restricted to older adults requiring mechanical ventilation who were able to participate in a CAM-ICU assessment. Because the investigator only spoke English, patients unable to speak and understand English were excluded.

Measures

The methods have been previously described in full in M. A Mulkey et al. (2019). In brief, hand-held EEG monitors (Ceribell Inc.) were placed on patients by the primary investigator. Continuous EEG (cEEG) data were then recorded for 2-hours for each of 4 consecutive days from each consented participant. Delirium assessments using CAM-ICU were obtained daily after the first hour of cEEG. Demographics and past medical history were obtained from the data available from the electronic medical record and were abstracted prior to discharge. Thirty-day mortality and acuity scores were obtained from administrative databases.

Electroencephalography (EEG)

Raw EEG data includes both brainwave and electrical activities from the heart, the eyes, electronic devices such as beds and telemetry monitoring, and EEG electrode motion interference called "ambient noise" or artifact. Prior to the analysis of the EEG data, those noise components must be filtered out of each channel using traditional high- and low-pass filters and advanced independent component analysis filters. Then, raw EEG signals from each channel can be subjected to power spectral density analysis to determine relative presence of 'high' and 'low' frequency components. By means of computational algorithms, EEG characteristics can be documented in an objective and quantitative way. Quantitative EEG (qEEG) relies on extensive technical knowledge in the field of digital signal processing and offers a wider spectrum of possible applications to analyze the data. Therefore, study data were evaluated using this method, known as spectral density analysis (Shinozaki et al., 2018).

Electrophysiologic signals characteristic of delirium are often reported as 'diffuse slowing,' meaning that the brain waves are of a reduced frequency. Therefore, the emergence of low-frequency waves indicates potential occurrence of delirium in the raw EEG. The fact that all EEG channels are able to detect the same reduction in frequency suggests that use of a small number of channels would be sufficient to obtain relevant data indicative of delirium.

Ceribell derived EEG utilizes 10 electrodes as opposed to traditional EEG that typically uses 21 electrodes. These 10 electrodes, that may be easily applied by non-experts such as nurses, produce 8 channels of EEG data that are combined with appropriate investigator developed mathematical algorithms to analyze EEG signals. Using ratios to reflect the relative presence of high- and low-frequency activity, EEG data are ready to be evaluated for the presence of delirium. Due to the objective nature of EEG, interrater reliability concerns seen with currently available bedside screening tools would not be a confounder. EEG can be strongly correlated with patient outcomes and may provide additional information for goals of care decisions (Shinozaki et al., 2019; Shinozaki et al., 2018). As a result, screening is practical, feasible and greatly facilitated.

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APPENDIX A: NOTIFICATION OF UMCIRB APPROVAL

ECU
EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
4N-64 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office 252 744 2914   Fax 252 744 2284   www.ecu.edu/ORIC/irb

Notification of Initial Approval (Committee)

From:	Biomedical IRB
To:	Malissa Mulkey
CC:	Sonya Hardin
Date:	4/6/2018
Re:	UMCIRB 17-001900 MIND

I am pleased to inform you that at the convened meeting on 3/14/2018 12:15 PM of the Biomedical IRB, the committee voted to approve the above study. Approval of the study and the consent form(s) is for the period of 3/14/2018 to 3/13/2019

The Biomedical IRB deemed this study Greater than Minimal Risk.

Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a continuing review/closure application to the UMCIRB prior to the date of study expiration. The investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace). The approval includes the following items:

Document	Description
HIPAA-Authorization-9-17--1.docx(0.02)	HIPAA Authorization
Informed Consent(0.02)	Consent Forms
MIND IRB PROPOSAL.docx(0.01)	Study Protocol or Grant Application
Nurse-Patient-Family Surveys(0.01)	Surveys and Questionnaires
Research Informaiton SHeet(0.01)	Consent Forms
Research Information Sheet(0.01)	Recruitment Documents/Scripts
Research Information Sheet(0.01)	Consent Forms
Variable Table.docx(0.01)	Data Collection Sheet

UMCIRB members were recused for reasons of potential for Conflict of Interest: None

APPENDIX B: PERMISSION FOR USE OF MANUSCRIPT

From: Kathleen Gould <kathleen.gould@bc.edu>
Date: July 8, 2020 at 2:10:25 PM EDT
To: mulkeym16@gmail.com
Subject: Fwd: An Item of Interest from Dimensions of Critical Care Nursing
Reply-To: kathleen.gould@bc.edu

Hi Melissa,
Yes of course you can use this work as long as you cite it as appearing in DCCN and present the
correct citation. As you may know, the article also allows viewers to see a slide deck of any
tables/figures, and certainly, you may want to use this slide and with Wolters Kluwer logo in any of
your presentations!
Congratulations on your success and continued work. Please consider reviewing or writing for us
again!

Best, Kathy

--
Kathleen Ahern Gould RN, MSN, PhD

Editor-In-Chief *Dimensions of Critical Care Nursing*
Lippincott Williams & Wilkins
Wolters Kluwer Health
http://journals.lww.com/dccnjournal/pages/default.aspx
dccneditor@wolterskluwer.com

Clinical/Adjunct Faculty Boston College
William F. Connell School of Nursing
gouldkc@bc.edu
617-827-2250

From: **Malissa Mulkey** mulkeym16@gmail.com
Subject: Published Article DCCN-D-19-00007 - Detecting Delirium Using a Physiologic Monitor
Date: June 23, 2020 at 3:14 PM
To: dccneditor@wolterskluwer.com
Cc: Laura Gantt ganttl@ecu.edu

Dr. Gould,
I am writing to inquire about obtaining permission to use this manuscript as one of the
manuscripts in my manuscript option Dissertation?
I would really like to use this article as it is representative of the work I have done for
dissertation.
Thank you, Malissa

APPENDIX C: VIDANT HEALTH LETTER OF SUPPORT

VIDANT HEALTH™

October 3, 2017

Dear Grant Reviewers,

This letter is being sent to confirm support of the research proposed by Malissa Mulkey. The proposed research will examine relationships in BIS-EEG data and delirium status based on the CAM-ICU in medical and surgical intensive care aging patients, an under-studied but important population of critically ill adults. The use of the CAM-ICU delirium tool has been well validated and currently is being widely used in ICUs.

The outcome measures chosen by Malissa and the research team (prevalence of delirium, validity of the BIS Index and BIS EEG waveform analysis- compared to gold standard impression of delirium measurement and limitations in detecting delirium) are valuable to advancing patient care, but are poorly studied. Further, investigation of delirium assessment in patients using BIS Index and EEG data has not yet been conducted in the U.S. As medical director and staff physician of the Medical ICU, I am excited that this proposal brings us an opportunity to find a more reliable way of detecting delirium. Better delirium detection may enhance tailored treatment options that abate its progression, minimize associated complications (such as prolonged hospital stays, time on a ventilator, ICU cost, and cognitive impairment at hospital discharge) and optimize short and long-term outcomes of patients surviving their critical injury.

We continually strive to manage the care of patients with critically illness with the highest quality care possible. The investigation of delirium in aging adult patients needs the attention of the critical care community. I anticipate that this study will not only offer valuable information about the ability and ease of detecting delirium in patients, but will also increase the interest in and momentum toward future investigation of delirium in other intensive care units.

Sincerely,

Jennifer Stahl, MD
Clinical Assistant Professor
Co-Medical Director Medical ICU
Vidant Medical Center
East Carolina University

Ogugua N. Obi, MD
Clinical Assistant Professor
Co-Director Medical ICU
Vidant Medical Center
East Carolina University

APPENDIX D: CAM-ICU WORKSHEET

CAM-ICU Worksheet
http://www.icudelirium.org/docs/CAM_ICU_training.pdf

	Positive	Negative
Feature 1: Acute Onset or Fluctuating Course Positive if you answer 'yes' to either 1A or 1B.	Positive	Negative
1A: Is the pt. different than his/her baseline mental status? Or 1B: Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (e.g. RASS*), GCS, or previous delirium assessment?	Yes	No
Feature 2: Inattention Positive if either score for 2A or 2B is less than 8. Attempt the ASE letters first. If pt. can perform this test and the score is clear, record this score and move to Feature 3. If pt. is unable to perform this test or the score is unclear, then perform the ASE Pictures. If you perform both tests, use the ASE Pictures' results to score the Feature.	Positive	Negative
2A: ASE Letters: record score (enter NT for not tested) Directions: Say to the patient, *"I am going to read you a series of 10 letters.* *Whenever you hear the letter 'A,' indicate by squeezing my hand."* Read letters from the following letter list in a normal tone. S A V E A H A A R T Scoring: Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."	Score (out of 10):_____	
2B: ASE Pictures: record score (enter NT for not tested) Directions are included on the picture packets.	Score (out of 10):	
Feature 3: Disorganized Thinking Positive if the combined score is less than 4	Positive	Negative
3A: Yes/No Questions (Use either Set A or Set B, alternate on consecutive days if necessary): Set A / Set B Will a stone float on water? / 1. Will a leaf float on water? Are there fish in the sea? / 2. Are there elephants in the sea? Does one-pound weigh more than two pounds? / 3. Do two pounds weigh more than one pound? Can you use a hammer to pound a nail? / 4. Can you use a hammer to cut wood? Score_(Patient earns 1 point for each correct answer out of 4) 3B: Command Say to patient: "Hold up this many fingers" (Examiner holds two fingers in front of patient) "Now do the same thing with the other hand" (Not repeating the number of fingers). *If pt. is unable to move both arms, for the second part of the command ask patient "Add one more finger) Score_(1 point if able to successfully complete the entire command)	Combined Score (3A + 3B): _ (out of 5)	
Feature 4: Altered Level of Consciousness (see also §) Positive if the actual RASS score is anything other than "0" (zero)	Positive	Negative
Overall CAM-ICU (Features 1 and 2 and either Feature 3 or 4):	Positive	Negative

§ Altered level of consciousness

Is the patient's level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor or coma?

Alert: Spontaneously fully aware of environment and interacts appropriately.

Vigilant: Hyperalert.

Lethargic: Drowsy but easily aroused, unaware of some elements in the environment or not spontaneously interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally.

Stupor: Difficult to arouse, unaware of some or all elements in the environment or not spontaneously interacting with the interviewer; becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subject lapses back into unresponsive state.

Coma: Unarousable, unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer so that the interview is impossible even with maximal prodding.

Purpose	To outline the nursing management of patients who demonstrate acute confused and disoriented behavior in intensive care unit. The goal is to support and protect the patient until the underlying causes are identified and treated.
Definition	Delirium is defined as a cerebral syndrome characterized by sudden onset, fluctuating course, and disturbance in consciousness, cognition, attention, and perception.
The essential features of delirium include:	fluctuating mental status throughout the day, often with worsened symptoms at night impaired attention and concentration disorientation to time, place, and/or person impaired memory (especially recall of recent events and formation of new memories) altered sleep-wake cycle noticeable increase or decrease of motor activity restlessness/ agitation (i.e., attempts to climb out of bed, removal of medical equipment, screaming or calling out, picking at the air) disorganized thinking hallucinations (usually visual) illusions (misinterpretation of sensory stimuli, e.g., shadows, real objects, persons, sounds) suspiciousness
Delirium is generally d/t underlying acute medical condition such as:	infection, fever adverse effects of medications pain drug or alcohol abuse/withdrawal dehydration and electrolyte imbalances hypoxia nutritional deficiencies

Important risk factor for delirium include:	advanced age
	pre-existing cognitive difficulties (brain damage or dementia)
	sensory impairment
	sleep deprivation
	acute drug withdrawal
	multiple physical illnesses
	anticholinergic medication, polypharmacy

RASS Scale

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

Procedure for RASS Assessment
Observe patient

1a: patient is alert, restless, or agitated. (score 0 to +4)

If not alert, state patient's name and *say* to open eyes and look at speaker.

Patient awakens with sustained eye opening and eye contact.   (score –1)
Patient awakens with eye opening and eye contact, but not sustained.   (score –2)
Patient has any movement in response to voice but no eye contact.   (score –3)

When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.

Patient has any movement to physical stimulation.   (score –4)
Patient has no response to any stimulation.   (score –5)
If RASS is -4 or -5, then Stop and Reassess patient at later time

(Sessler et al., 2000)

APPENDIX F: INFORMED CONSENT

East University

Carolina

Informed Consent to Participate in Research
Information to consider before taking part in research that has no more than minimal risk.

Title of Research Study: Methods of Identifying Neurological Delirium
Principal Investigator: Malissa Mulkey   (Person in Charge of this Study)
Institution, Department or Division: East Carolina University, College of Nursing
Address: 600 Moye Blvd, Greenville, NC
Telephone #: 919-495-5966
Participant Full Name: _____
Date of Birth: _____   Please PRINT clearly

Researchers at East Carolina University (ECU) and Vidant Medical Center study issues related to society, health problems, environmental problems, behavior problems and the human condition. To do this, we need the help of volunteers who are willing to take part in research.

Why am I being invited to take part in this research?
The purpose of this research is to find out if we can see changes in the brain's electrical activity that are caused by delirium. You are being invited to take part in this research because you are a patient in the Medical or Surgical Intensive Care Unit, 50 years old or older, and need a ventilator to help you breathe. The decision to take part in this research is yours to make. By doing this research, we hope to learn whether a special type of monitor, the Ceribell monitor, can help nurses and providers know their patients are developing delirium earlier. If this monitor can pick up these changes, we might be able to treat it earlier. This would improve patient care and might decrease time in the hospital. If you volunteer to take part in this research, you will be one of about 30 people to do so.

Are there reasons I should not take part in this research?
I understand I should not volunteer for this study if I am, under 50 years of age, cannot understand what others are saying, have a new brain injury (symptoms started less than 72 hours ago) or if I know my doctor is going to take me off the breathing machine (ventilator) in the next 12 hours. If I have had a seizure or my provider thinks I may have had a seizure in past 24 hours

What other choices do I have if I do not take part in this research?
You can choose not to participate.

Where is the research going to take place and how long will it last?
The research will be conducted at Vidant Medical Center in the Medical and Surgical ICU. You will need to be a patient in the Medical or Surgical ICU, *if possible,* up to 4 days during the study. The total amount of time you will be asked to volunteer for this study is 4 days over the next 6 months.

What will I be asked to do?
You will be asked to do the following:
You will be assigned a research number. All information collected from you will include this research number. It will not have your name or information that will identify you.
You will have sensors that look like white stickers applied to your forehead for up to 4 days while in the ICU.
The sensors will be connected to a monitor with a cable to monitor your brain's electrical activity,

similar to a heart monitor.
If you are discharged from the ICU within those 4 days, the sensors will be removed and the monitoring will be stopped.

If you are still in the ICU after 4 days, the sensors will be removed and the monitoring will be stopped. Each morning, for the same 4 days, a nurse will visit you in your room. He or she will ask you to answer a few word association questions, to hold up fingers with one or both hands, and to squeeze their hand a few times. Ex. Will a stone float on water? Squeeze my hand every time you hear me say the letter "A." You can agree to opt out of these assessments and this monitoring at any time. If you opt out only the data collected up to that time will be used in the study. No further monitoring or assessments will be performed.

What might I experience if I take part in the research?
The only possible risk associated with this research are a possible local rash or irritation at the sensor site if you are allergic to the adhesive or a skin tear if you abruptly pull the sensors off. We do not know of any other risks (the chance of harm) associated with this research. Any risks that may occur with this research are no more than what you would experience in everyday life. You will not personally benefit from taking part in this study. There may not be any personal benefit to you but the information gained by doing this research may help others in the future.

Will I be paid for taking part in this research?
We will not be able to pay you for the time you volunteer while being in this study.
Your bill for care or services provided by the medical center will not be free or discounted because of participation in this study.
Your medical care will not change because of participation in this study

Will it cost me to take part in this research?
It will not cost you any money to be part of the research. You will receive a bill for medical care provided.

Who will know that I took part in this research and learn personal information about me?
ECU and the people and organizations listed below may know that you took part in this research and may see information about you that is normally kept private. With your permission, these people may use your private information to do this research:
Any agency of the federal, state, or local government that regulates human research. This includes the Department of Health and Human Services (DHHS), the North Carolina Department of Health, and the Office for Human Research Protections.
The University & Medical Center Institutional Review Board (UMCIRB) and its staff have responsibility for overseeing your welfare during this research and may need to see research records that identify you.
People designated by Vidant Medical Center, Vidant Health, your health care team, and the research team will see this information or know you are participating in this study.
Because you are a patient at Vidant Medical Center, a copy of the first page of this form will be placed in your medical records.

How will you keep the information you collect about me secure? How long will you keep it?
The information collected by the monitor will be downloaded to a jump drive (USB) each day. This information will be transferred and stored on a secure password protected computer. Only the research team will see this information.
Whether you answer the questions correctly, hold up the correct number of fingers and how many times you squeeze at the wrong time will be written down on a case report form. This information will be

stored in a notebook in a locked cabinet that is inside a locked office. Your name and information that will identify you will not be written on this form. Only the research team will see these forms.

When the research study is finished and information is no longer needed it will be destroyed by deleting the information from the thumb drive (USB) and computer files.

The information may be stripped of personal and patient identifiers and used in future research without anyone knowing it is information from you.

What if I decide I do not want to continue in this research?

You can stop at any time after it has already started. There will be no consequences if you stop and you will not be criticized. You will not lose any benefits that you normally receive.

Who should I contact if I have questions?

The people conducting this study will be able to answer any questions concerning this research, now or in the future. You may contact the Principal Investigator at 919-495-5966 Monday through Friday from 9am – 5pm.

If you have questions about your rights as someone taking part in research, you may call the Office of Research Integrity & Compliance (ORIC) at phone number 252-744-2914 (days, 8:00 am-5:00 pm). If you would like to report a complaint or concern about this research study, you may call the Director of the ORIC, at 252-744-1971 and the Vidant Medical Center Risk Management Office at 252-847-5246.

I have decided I want to take part in this research. What should I do now?

The person obtaining informed consent will ask you to read the following and if you agree, you should sign this form:

I have read (or had read to me) all of the above information.

I have had an opportunity to ask questions about things in this research I did not understand and have received satisfactory answers.

I know that I can stop taking part in this study at any time.

By signing this informed consent form, I am not giving up any of my rights.

I have been given a copy of this consent document, and it is mine to keep.

_____   _____   _____

Participant's or Authorized Representative Name   Signature   Date

 _____

Relationship to the Patient

Person Obtaining Informed Consent: I have conducted the initial informed consent process. I have

orally reviewed the contents of the consent document with the person who has signed above and

answered all of the person's questions about the research.

_____

Person Obtaining Consent (PRINT)   Signature   Date

_____

Principal Investigator   (PRINT)   Signature   Date

(If other than person obtaining informed consent)

APPENDIX G: RESEARCH INFORMATION SHEET

Research Information Sheet

Can Delirium be identified on Ceribell EEG Monitors?
<u>Background Information</u>
You are one of about 30 people in the Intensive Care Unit (ICU) being asked to take part in a research study. This research is trying to find out if confusion can be identified on a monitor called the Ceribell Monitor. As a patient in the ICU, you qualify to be part of this research. This sheet tells you about the research, risks/benefits, and its confidential and voluntary nature. Please read this sheet before agreeing to take part in the research. If you have any questions, you can contact the researcher, Malissa Mulkey MSN, RN, at (919) 684-5652 or 919-495-5966. If you have questions about your rights as a research subject, you should contact the Institutional Review Board (IRB) at (252) 744-2914. You can also contact the IRB if you have concerns or complaints about the research, if you cannot reach the researcher, or if you want to talk to someone other than the researchers.

<u>Purpose</u>
This research will help us learn how confusion looks on a monitor. This may help us improve our care of ICU patients with confusion. You will be assessed for confusion by a research nurse and your care team for 4 days. Sensors (stickers) will be placed on your forehead for 4 days.

<u>Who can participate?</u>
If you are 65 years old or older, a Medical or Surgical ICU patient, and need a ventilator (respirator) to breathe.

<u>Who cannot participate?</u>
If you are too sleepy to participate, do not speak English, cannot understand what people are saying, your doctor plans remove the ventilator (respirator) in the next 12 hours, you have had a seizure in the last 24 hours, or have a new brain injury in the last 3 days.

<u>Time Involved</u>
You will need to wear sensors on your forehead 2 hours each day for 4 days. Sensors will be removed if you are transferred out of the ICU.

<u>Risks of being in the research</u>
Risks from being in this research are rare. Risks include a possible rash or skin tear on the forehead where stickers are placed. At any time, you can decide to not to take part in the research. If you experience emotional distress from being in the research, you can contact the IRB for help. There is a rare chance someone might access your information without permission.

<u>Benefits of being in the research</u>
There are no rewards or payment for being in this research. Your data might help us learn how often confusion occurs and how to assess for it. These facts may help other patients.

<u>Confidentiality</u>
Your data is confidential. Your name will not be on documents or reports. A research number will be used to identify you. Data will be stored on a secure computer. Only the research team will have access to your data.

Voluntary nature of the research

Taking part in this research study is voluntary. Refusing to take part will not be held against you. You can withdraw at any time, for any reason. After reading this sheet, you can (1) agree to take part or (2) decide to not to take part.

APPENDIX H: RESEARCH PROTOCOL

Research Protocol

1. Bedside RN will approach patient and/or LAR to determine possible interest in participation in a research study.

2. Bedside RN will notify the research team of a potential participant.

3. PI will approach patient and/or LAR to discuss research and obtain consent. (SCRIPT)

4. PI will notify nurse and provider of enrollment and label chart identifying patient is in a research study. (SCRIPT)

5. Research RN will bring Ceribell research monitor to bedside.

6. Ceribell EEG headband will be applied to the patient's forehead, sensors will be connected to monitor and monitor will be turned on. (SCRIPT)

7. Accuracy of EEG data with minimal artifact (determined by evaluating EEG waveform on Ceribell monitor for artifact and signal strength) will be determined by the research RN.

8. Each day, one hour prior to CAM-ICU assessments, the research RN will place Ceribell headband around the patients and EEG quality.

9. The Research RN will complete CAM-ICU assessments each morning for four days. (SCRIPT)

10. If the participant is on sedation, the CAM-ICU will be assessed during the morning sedation vacation when sedation is turned off or minimized.

11. One hour after CAM-ICU assessment, the PI will remove Ceribell headband from patient.

12. If redness, rash, or any disruption in skin integrity at lead sites is observed, the Ceribell monitor will immediately be disconnected and the sensor will be removed. The provider will be notified. The patient will be disenrolled in the study. Data collected to that point will be utilized for analysis. (SCRIPT)

13. At the end of day four, the Research RN will disconnect the Ceribell monitor and remove the sensor.

Research RN will discard disposable sensors, turn monitor off, and remove monitor from patient care area and clean monitor per industry standard. (SCRIPT)

Variable Table

Variables	Definition	Source
Delirium Status	0=CAM-ICU 1=CAM-ICU +	CAM
Raw EEG waveform data	4 EEG waveforms	Ceribell
Alpha theta ratio	Ratio of awake (alpha) waves to asleep (theta) waves	Ceribell
Alpha wave frequency and strength	Strength measured in Hertz; Frequency in %	Ceribell
Theta wave frequency and strength	Strength measured in Hertz; Frequency in %	Ceribell
Delta wave frequency and strength	Strength measured in Hertz; Frequency in %	Ceribell
RASS Scores	-5=unarousable; -4=Deep sedation; -3=Moderate sedation; -2=Briefly awakens to voice (<10 sec); -1=Not fully alert (>10 sec); 0=Alert & calm +1=Restless; +2=Agitated (non-purposeful) +3=Very agitated (aggressive/pulls at tubes); +4=Violent	EHR
Hospital Length of stay	Days	EHR
Admission Date`	Date	EHR
ICU length of stay	Days	EHR
Insurance Type	1=commercial; 2=Medicaid; 3=Medicare; 4=Self Pay; 5=Workman's Comp ; 6=unknown	EHR
Legally Authorized Representative	1=spouse; 2=child; 3=parent; 4=sibling; 5=aunt/uncle; 6=other	EHR
Independent confounding variables		
Level of Consciousness	List	EHR
GCS Score	List	EHR
Age	Age in years	EHR
Race	1=White; 2=Black; 3=Hispanic/Latino; 4=native American; 5=Pacific Islander 6= Alaskan Native; 7=other	EHR
Gender	1. Male, 2. Female	EHR
Marital status	1. Separated, 2. Divorced, 3. Widowed 4. Never Married 5. Cohabitation	EHR
Medical & Surgical History	List	EHR
Primary & Secondary Diagnoses	List	EHR
APACHE mean	Number; collected within 24 hrs. of admission	EHR
Length of time on vent	Day	EHR
Restraint use	0=no; 1=yes	EHR
Discharge disposition	0=death; 1=home; 2=rehab; 3=SNF; 4=LTC;	EHR

30-day mortality	0=dead; 1=alive	Social Security Index
Living situation at admission	1=independent; 2=institution	EHR
Living situation at discharge	1=independent; 2=institution	EHR
Smoking status	0=no; 1=yes; 2=ex-smoker	EHR
ETOH use	0=no; 1=yes	EHR
Substance Use	0=no; 1=yes	EHR
If substance use =yes then Substance used	List	EHR
Comorbidities Charlson Comorbidity Form	List	EHR
Medications (ex. Anti-hypertensive, Peptic Ulcer prophylaxis, Benzodiazepines)	List	EHR

Charlson Comorbidity Index

Check the **medical conditions/diseases** the patient has. Mark yes or no for each item listed).

Condition	Yes	No
Myocardial Infarction/heart attack	____	____(1)
Congestive heart failure	____	____(1)
Peripheral Vascular disease	____	____(1)
Cerebral vascular accident (stroke)/or TIA	____	____(1)
Hemiplegia/paraplegia (in arms or legs due to stroke)	____	____(2)
Chronic obstructive pulmonary disease	____	____(1)
Ulcer disease	____	____(1)
Diabetes	____	____(1)
Complications from diabetes-affecting eyesight nerve sensations and / or kidney disease	____	____(1)
Moderate/severe renal disease	____	____(2)
Connective tissue disease (lupus, rheumatoid arthritis, polymyositis	____	____(1)
Dementia, Alzheimer's disease	____	____(1)
Chronic hepatitis; cirrhosis	____	____(1)
Cirrhosis	____	____(3)
AIDS	____	____(6)
Leukemia	____	____(2)
Lymphoma	____	____(2)
Cancer (not skin, leukemia or lymphoma) w metastasis	____	____(6)
Cancer (not skin, leukemia or lymphoma) w/o metastasis	____	____(2)

TOTAL SCORE_____

CATEGORY (Score of 1-2 = 1; 3-4= 3; 5 or more = 5): _____

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases, 40*(5), 373-383