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Master's Thesis

Mismatch Negativity and General Anesthesia

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Declaration of Authorship

I, Richard KOLESAR, declare that this thesis titled, "Mismatch Negativity and General Anesthesia" and the work presented in it are my own. I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University.
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- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
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"Judge a man by his questions rather than by his answers"

Voltaire

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Abstract

Faculty of Science
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Master of Science

Mismatch Negativity and General Anesthesia

by Richard KOLESAR

In order to further explore the nature of anesthesia-induced unconsciousness and its relationship to nociception, investigators attempted to determine whether mismatch negativity could be detected during general anesthesia and surgery. An auditory odd-ball paradigm designed to elicit mismatch negativity was presented to ten patients during general anesthesia and surgery. Five of the ten also underwent testing in the awake state prior to surgery. Multiple EEG recordings were obtained in each patient and each condition using the BioSemi ActiveTwo 64 EEG electrode system. The anesthetic regime required only that 0.7 MAC of an inhaled agent was administered. Several methods of analysis were utilized to determine whether an MMN response could be identified: visual inspection of ERP waveforms, targeted t-tests, cluster permutation tests, and multivariate pattern analysis. Whereas deviant-related negativity was readily detected in the awake state, deviant-related negativity was not detected during surgery and general anesthesia. Results demonstrate that essential components of the MMN response are abolished during typically conducted general anesthesia even with significant surgical stimulation. These results are consistent with previous research on ERPs and anesthesia. Results cast doubt on the possibility of sensory memory related to intraoperative events.

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List of Abbreviations

ACh	**A**cetyl**Ch**oline
AUC	**A**rea **U**nder the **C**urve
AEP	**A**uditory **E**voked **P**otential
ASSP	**A**uditory **S**teady **S**tate **P**otential
BIS	**BiS**pectral Index
CAS	**C**anadian **A**nesthesiologist's **S**ociety
ECoG	**E**necephalocorticography
EEG	**E**lectroencephalography
ERAN	**E**arly **R**ight **A**nterior **N**egativity
ERP	**E**vent **R**elated **P**otential
ETAC	**E**nd **T**idal **A**nesthetic **C**oncentration
HCN	**H**yperpolarization **C**yclic **N**ucleotide
GA	**G**eneral **A**nesthesia
GABA	**G**amma**A**mino**B**utyric**A**cid
GFP	**G**lobal **F**ield **P**ower
ICU	**I**ntensive **C**are **U**nit
LLAEP	**L**ong **L**atency **A**uditory **E**voked **P**otential
MAC	**M**imimum **A**lveolar **C**oncentration
MLAEP	**M**id**L**atency **A**uditory **E**voked **P**otential
MMN	**M**is**M**atch **N**egativity
MVPA	**M**ulti**V**ariate **P**attern **A**nalysis
MOAAS	**M**odified **O**bserver's **A**ssessment of **A**lertness and **S**edation Scale
NMDA	**N-M**ethyl**D-**asparticAcid
REB	**R**esearch **E**thics **B**oard
ROC	**R**eceiver **O**perator **C**urve
RS	**R**amsey **S**edation Scale
SPL	**S**ound **P**ressure **L**evel
TCI	**T**arget **C**ontrolled **I**nfusion
TMS	**T**ranscranial **M**agnetic **S**timulation
UWS	**U**nresponsive**W**akefullness**S**yndrome

Dedicated to my wife, Patricia. . . .

Chapter 1

Introduction

1.1 Purpose

Over the last 50 years our understanding of the biophysical properties and cellular actions of anesthetic drugs has greatly expanded. Exactly how these properties and actions result in unconsciousness is still incompletely understood. The most obvious impediment to better understanding this state is the amnesia and immobility that invariably accompanies the anesthetic state. Therefore, much of what we now understand is derived indirectly from studies using neuroimaging and electrophysiology. In gross terms the former provides a spatial perspective while the latter provides a temporal perspective into the cognitive processes involved in losing and regaining consciousness. Both investigative tools now inform current leading theories of consciousness which, for the most part, involve brain network connectivity. High definition electroencephalography (EEG) is arguably the most powerful and accessible electrophysiological tool for elucidating network dynamics. However, the event related potential (ERP) technique continues to provide insight into nature of consciousness by tracing the course of neural events on the millisecond timescale.

The purpose of this study is to investigate the extent of auditory sensory processing during surgery and general anesthesia. Its main goals are twofold: one, to determine whether mismatch negativity (MMN), a specific ERP which is a biomarker of auditory cortical processing, can be detected during routine surgery and general anesthesia; and, two, if detectable, determine whether this marker is consistently or only transiently present. Since it is one the first studies of this sort conducted during surgery, it also provides opportunity to assess whether surgery itself can effect cortical responses and to describe some

of the challenges that accompany measurement of microvolt responses in the modern operating room.

1.2 Relevance

1.2.1 Anesthesia and Surgery

Approximately 2.5 million surgical procedures are performed each year in Canada (OECD, 2017; Picard, 2014). Though precise data are lacking, many, if not most, of these procedures involve general anesthesia (GA). Understandably, surgical patients expect to be unconscious during surgery (Rowley et al., 2017) and want assurance that the effects of GA are transient and reversible (Cole-Adams, 2017). At this time, the nature of consciousness is poorly understood; and so, guaranteeing lack of it is problematic. Anecdotes suggest that some patients are "never the same" after major surgery. Given the rising demand for surgical services and our aging population, much more research is needed to better address the gaps between what patients expect and need, and what current medical practice delivers.

Knowledge gaps and methodological limitations persist due to: inadequate understanding of underlying pathophysiology, lack of validated and standardized preoperative assessment tools, inadequate monitoring technology, and lack of biomarkers (Vlisides, 2019). Of note, inadequate understanding of how the brain generates consciousness has hindered development of a useful intraoperative monitor of unconsciousness. The direct consequences of our inability to objectively differentiate the conscious and unconscious state can result in both inadequate anesthesia (resulting in awareness, for example) and excessive anesthesia (resulting in post-operative cognitive dysfunction, for example). Traditional approaches based on phenomenal description of brain states are unlikely to yield useful results (Vlisides, 2019). Elucidation of the true neural correlates of consciousness will require new perspectives and new technologies applied to the study of the human brain, the primary motivation for the present work. Translation of this science into clinical practice will directly impact the way anesthetics are delivered and lead to new, safer, anesthetic techniques.

1.2.2 Disorders of Consciousness

Understanding the neurobiology of consciousness remains one of the greatest challenges of modern science; and field experts generally agree that investigation into disorders of consciousness is both revealing and essential (Mashour, 2006). Some researchers argue that consciousness (or lack of it) can be explained by specific, biologically grounded "neural correlates", and that any unified theory of (un)consciousness must explain all alterations of consciousness, whether based in pharmacology, physiology, or pathology (Koch et al., 2016). In this way, research into anesthesia induced unconsciousness overlaps with other "disorders" of consciousness: sleep and coma (Brown, Lydic, and Schiff, 2010). Whereas underlying pathophysiology may differ, experimental approaches use similar techniques and methods including both fMRI and EEG. These neurophysiologic studies tend to focus on network connectivity and evoked responses (ERP and TMS, e.g.), though specific techniques understandably differ (Boveroux et al., 2008). Therefore, experimental findings in any one condition ought to inform theories of consciousness; and methodolgical advances should benefit present and future consciousness research.

1.2.3 ERP Research

As outlined below, the "ERP" technique evolved years after Berger's discovery of the EEG in 1929. Since the first description of the evoked response called "mismatch negativity" by Butler in 1968 (Butler, 1968), interest in the measurement, underlying neural components, and significance of this response has grown and remains highly visible in scientific publications. Mismatch negativity (MMN), also described as the "novelty response" in some studies, is considered to be a biomarker of consciousness (Näätänen et al., 2007). Notably, it serves as an outstanding example of "predictive coding," hierarchical processing," and the Bayesian brain," prominent themes in contemporary cognitive neuropsychology (Garrido et al., 2009). Clearly, investigation into anesthesia-induced unconsciousness using the ERP technique, in general, and the MNN, specifically, expands understanding of the MMN itself. This investigation also highlights some the classic problems in MMN work - namely, the (low) signal to noise ratio, the multiple comparison problem, and processing of single subject data at the epoch level. These issues are critical to real world applications such as brain computer interfaces and clinical

monitoring systems. The current investigation reappraises the relationship of the MMN to the conscious brain, and, as well, proposes opportunities and challenges for future research in this area.

1.3 Background

1.3.1 ERPs and Consciousness Research

Why use ERPs to study consciousness? Functional connectivity studies utilizing either fMRI or EEG currently dominate the field (Bonhomme et al., 2019). Most of these studies focus on network connectivity and dynamics and aim to demonstrate various differences between the conscious and unconscious state. On a practical level , performing surgery in an MRI scanner is simply not possible. On a theoretical level, Logothetis raises "red flags" about drawing conclusions from fMRI data when the neurobiology is uncertain (Logothetis, 2008). Based on the fact that hemodynamic responses, which form the basis of the BOLD signal, are sensitive to the size of the activated population, he concludes:

> "The fMRI signal cannot easily differentiate between function-specific processing and neuromodulation, between bottom-up and top-down signals, and it may potentially confuse excitation and inhibition. The magnitude of the fMRI signal cannot be quantified to reflect accurately differences between brain regions, or between tasks within the same region."

Yet attempts to use fMRI to investigate anesthesia-induced unconsciousness and cortical processing are published (Plourde et al., 2006; Alkire, 2008; Palanca, Avidan, and Mashour, 2017; Boveroux et al., 2010; MacDonald et al., 2015; Uhrig et al., 2018; Demertzi et al., 2019) and continue to shape our thinking about consciousness. Similar studies using high definition EEG actually comprise the bulk of recent scientific publications in this area. Remarkably, despite use of advanced imaging technologies and analytical methods, the nature of anesthesia-induced unconsciousness is still poorly understood, mainly because of the confounding of state-related and drug-related effects (Pal et al., 2020). Pal's animal study, for example, demonstrated that wakefulness can be dissociated from cortical connectivity. Shahaf suggests that, given the complexity of the nature of consciousness,

focusing on the neurophysiology of behavioral processes that underlie consciousness - rather than consciousness itself - is more likely to yield desired results (Baron Shahaf, Hare, and Shahaf, 2020). These processes are perception and attention. These processes are embedded in the EEG signal and are easily accessible as ERPs. Early evoked responses in the 50 -200 ms range inform understanding of perceptual processes, while later responses up to 600 ms inform understanding of attentional processes. Accordingly, abstract discussion of neurophysiologic markers of consciousness are replaced with the more concrete markers of perception and attention which support conscious experience. Conceptually, this approach also embodies study of bottom-up (sensation) and top-down (memory) processes. Such an approach involves assumptions, such as a congruous relationship between consciousness, attention and memory; but this assumption in not unreasonable. Most importantly, ERPs are an easily accessible tool to study the impact of anesthesia and surgery on the various cognitive processes that comprise consciousness.

1.3.2 Mismatch Negativity

This research focuses on mismatch negativity for two main reasons: (1) it is a "taskless" ERP; and (2) it is a late latency ERP (or at least components of it are late latency), which implies that it plays some role in perception in addition to mere sensation. During general anesthesia subjects are immobilized and therefore unable to perform any task involving a motor response. Indeed, some researchers (detailed below) have utilized task paradigms, such as the P3 response, to study general anesthesia , but these studies have focused more on the transitions between states rather than the unconscious state itself (see Chapter 2). Finally, since early and mid-latency evoked potentials largely reflect sensory processing at the level of the brainstem and thalamus, studies focused on these responses will unlikely provide new insights into the extent of cortical activity and cognitive processing during general anesthesia.

The traditional MMN was defined by Näätänen (Näätänen and Picton, 1987) and refined in subsequent studies and reviews (Näätänen et al., 2007, e.g.). The MMN is generated by the brain's response to a change in sensory stimulation. Identifying a change in the environment is a basic neurophysiologic function, which at a behavioral level, (re-)orients attention. This change is typically elicited in the laboratory by providing subjects with a stream of "standard"

stimuli with randomly dispersed "deviant" stimuli known as an "oddball" paradigm. The response is seen on the electroencephalogram as a negative deflection which is maximal in frontal or fronto-central scalp electrodes when referenced to the mastoids. The MMN usually peaks at 150-250 ms after the stimulus. Näätänen states that the auditory response consists of two components: a relatively early component generated by the bilateral superior temporal lobes, and a late component generated by the right inferior frontal cortex. Modern imaging techniques confirm his description of the MMN's functional anatomy. The relationship of the N1 response, which is synonymous with activation of primary sensory cortex, to the MMN is not straightforward; nonetheless, because of overlap of latencies, the MMN is often visualized as a difference wave obtained by subtracting the (average) deviant response from the (average) standard response. Näätänen's early work demonstrated that the MMN can be elicited in the absence of attention, and this "automatic" feature of the MMN is a defining feature. Although an MMN response can be observed in all sensory modalities (Näätänen et al., 2007), subsequent discussion will focus on auditory sensory processing which is the easiest to study in patients under general anesthesia.

The neurophysiologic interpretation of this response is still debated. A comprehensive review is beyond the scope of this thesis (see Fishman, 2014), but broadly three theories dominate current discussions. Näätänen's original interpretation maintains that the MMN is a discrimination process where the deviant event is found to be discongruent with the memory representation of the preceding stimuli (even in the absence of attention)." The memory trace of preceding sensory input is key to this interpretation. Another interpretation (May and Tiitinen, 2010) argues that the MMN results from "fresh" afferents which are not adapted (i.e. suppressed) by the standard steam. According to this "adaptation" hypothesis, the MMN is simply a difference wave between the N1 generated by the two different population of neurons. Cleverly constructed paradigms, source localization, and pharmacologic studies are just some of the kinds of evidence that have been used to assess the validity of these theories. However, Garrido (Garrido et al., 2009) combines elements of both the memory and adaptation models into a third model called "predictive coding" or hierarchical inference." Prediction-errors generated by the interaction of bottom-up and top-down streams are passed up the processing hierarchy. Depending on the weight of these prediction-errors,

determined by an adaptive or neuro-plastic process, changes in cortical connectivity occur to enhance the precision of top-down predictions. According to this theory, the MMN "represents a failure to predict bottom-up input and consequently a failure to suppress prediction error." Clearly, the memory-trace and predictive coding models have greater relevance to understanding the anesthetized brain. If either interpretation of the MMN is correct, then ability to elicit an MMN response during general anesthesia would imply cortical activity associated with the conscious brain.

What "automatic" or "pre-attentive" actually means is another topic of debate. Näätänen argues that this feature of the MMN response is unique and defining because it could be elicited in comatose patients, in healthy people during some stages of sleep, and in newborns who naturally have undeveloped nervous systems. May, on the other hand, refutes this claim with studies that show that attention modulates the MMN and can even abolish it. As well, he summarizes the then extant body of cognitive science that deals with attention and perception and concludes:

> "Attention clearly affects all stages of auditory sensory processing. There seems to be no specific location in the auditory pathway that forms the border between automatic and nonautomatic processing, and so the effect of attention is not a division of the pipeline of auditory processing into pre- and postattentive sections."

Recently, this debate has been reframed as whether the MMN requires "perceptual awareness." Using a sophisticated masking technique, Dykstra (Dykstra and Gutschalk, 2015) demonstrated that the MMN is observed only when the standard stream was consciously perceived. While admitting that teasing out the effects of attention versus awareness can be difficult, he offers arguments that on balance favor the concept that awareness - not attention - underlies the mechanism of the MMN response. Therefore, the MMNs recorded in patients with disorders of consciousness would require at least "partial" perceptual awareness despite lack of confirming behavioral signs of it. This interpretation is highly relevant to the current study where the extent of sensory processing under general anesthesia is investigated and issues of attention are not directly relevant.

1.3.3 General Anesthesia

The administration of medication to render a patient insensitive to surgery was termed "general anesthesia" by Holmes in 1846 following Morton's demonstration of the use of dimethyl ether during excision of a neck mass at the Massachusetts General Hospital the same year [1]. The definition has since been refined by Brown: "general anesthesia is a drug-induced reversible state consisting of unconsciousness, amnesia, antinociception, and immobility, with maintenance of physiologic stability" (Brown, Pavone, and Naranjo, 2018). Used in combinations known as "balanced general anesthesia," different drugs target specific behavioral endpoints: e.g. intravenous hypnotics or halogenated ethers for unconsciousness, benzodiazepines for amnesia, opioids for antinociception, and acetylcholine receptor blockers for immobility - though the actions of these various drug classes overlap to greater or lesser extent. Thus, general anesthesia is typically initiated in adults as a series of injections. Most of these drugs are extremely short acting, so the anesthetic state needs to be maintained by intermittent injections or by continuous infusions or ventilation with inhaled agents. Reversal of the state is achieved passively by ceasing administration of anesthetizing drugs and facilitating the normal physiologic processes that eliminate them. Except when drugs are administered by computerized pumps that incorporate elaborate pharmacokinetic models (TCI e.g.), plasma levels of anesthetic drugs vary somewhat unpredictably throughout the course of surgery. Medications are often administered in anticipation of or in reaction to surgical events - specifically events that trigger a nociceptive response. Nociception, which is a physiologic response to tissue injury (as opposed to "pain" which is the conscious perception of it), causes harmful hemodynamic and neuroendocrine responses that lead to organ failure and chronic pain. So-called "nociceptive breakthrough," occurring when the intensity of surgical stimulation exceeds the suppressive effects of the anesthetic drugs, is common during every type of surgery; and management of the nociceptive response is one of the primary preoccupations of the anesthesiologist.

While huge strides in understanding how anesthetics produce unconsciousness occurred in the 175 years following Morton's demonstration, many issues remain unresolved (Bonhomme et al., 2019; Hemmings et al., 2019). At the cellular level anesthetics interact with cell surface proteins to modulate neurotransmission. These drugs are believed to interact with more than 300

known proteins (and likely additional unknown ones). $GABA_A$, NMDA, 2-pore K, HCN, and ACh receptors all have established roles. At the circuit level much less is known. Multiple lines of investigation propose that anesthetics cause a disruption of thalamocortical connectivity as well as fronto-parietal directed connectivity; but proving a causal relationship between changes in connectivity and consciousness remains elusive. Most studies use unresponsiveness as a surrogate marker of unconsciousness, and they are almost certainly not equivalent neurocognitive states. Even interpretation of the most consistently observed changes in the scalp EEG and spectrogram - anteriorization of alpha power - are questioned due to the presumed minor role of frontal cortex in generating consciousness (Boly et al., 2017). Whereas return of the consciousness was once thought to be the reverse of loss of consciousness, increasing evidence suggests that emergence from anesthesia-induced unconsciousness involves activation of sub-cortical arousal pathways in the brainstem, hypothalamus, and basal forebrain (Nir et al., 2019; Kelz et al., 2019). Anesthesia-induced unconsciousness may not be a unitary state after all; many different alterations of the connectome may lead to the observable behavioral features of general anesthesia.

The relationship of arousal (wakefulness), consciousness, and nociception is a key to this thesis. Numerous imaging studies confirm that nociception predominantly activates hypothalamus and periaqueductal gray area of the brain (Brooks and Tracey, 2005; Leone et al., 2006). Imaging also implicates prefrontal, insular, anterior cingulate, and posterior parietal cortex (Lichtner et al., 2018). All these structures play a role in mediating arousal; and the latter three have also been touted as neural correlates of consciousness (Alkire, Hudetz, and Tononi, 2008). Critically, drugs that mitigate nociception tend to reduce arousal (Lydic and Baghdoyan, 2005; Brown, Pavone, and Naranjo, 2018). Opioids, which classically exert effects on the periaqueductal gray area of the descending inhibitory pain pathway, diminish arousal by inhibiting brainstem cholinergic circuits, median pontine reticular formation, and thalamus. Ketamine, an extremely potent NMDA blocker acting principally on dorsal horn neurons, decreases arousal by blocking excitatory glutaminergic circuits in parabrachial nucleus, median pontine reticular formation, thalamus, and basal forebrain. The point is this: nociception causes arousal and antinociception causes sedation. Whether nociception that escapes pharmacologic suppression can induce sufficient arousal to engage higher

cortical structures is a question posed in this research. Surgical stimulation models the nociceptive response, the MMN models cortical activation, and the experimental setting is general anesthesia.

[1]Typical of the times, original reports describing these events appeared in local newspapers - not scientific journals. The earliest reference in a trade publication to Morton's demonstration appeared in HJ Bigelow's article on inhalational anesthesia in the Boston Medical and Surgical Journal, 1846 (35), p. 309-317.

Chapter 2

Review of Literature

2.1 Introduction

What follows is a curated, not comprehensive, review of studies relevant to the MMN response and general anesthesia. Studies that specifically looked at the MMN during any kind of sedative or hypnotic drug administration are included. Similarly, studies that specifically focused on long latency ERPs, but not the MMN, are included if they included recordings during general anesthesia. Because this research is motivated by the need to better understand the nature of anesthesia-induced consciousness, some very notable ERP studies of drug-induced amnesia and ketamine based models of schizophrenia are not reviewed. All good studies build on the work of others; but, understandably, the sum total cannot be reasonably reviewed in the present context. Hopefully, this review will successfully convey the rich history of this line of research and highlight the most significant past and present contributions.

A few introductory notes may help those unfamiliar with ERPs. All published studies adhere to conventional ERP nomenclature. The initial letter refers to the polarity of the post-stimulus amplitude - positive, "P", or negative, "N" . The number following this letter refers to either the ordinal number of the deflection (in the series of post-stimulus deflections of same polarity) or latency in milliseconds. Additional lower-case letters following the number may further distinguish the ERP with regard to within-family subtype (e.g. P300*a*). A very general description of the ERPs referenced below is included in Appendix B). As noted in Appendix B, exact characterization of these ERPs can be difficult without consideration of the experimental context in which they arise. Reviewed studies also refer to standardized scalp electrode designations and locations. These are shown in the graphic in Appendix D which displays a

variant of the international "10-20" layout. In the studies below, the most commonly used scalp electrodes are located front to back (frontal, F; central, C; and parietal, P) in the anatomical saggital plane (central, z). Finally, commonly used behavioral scales of alertness are shown in Appendix A. These few notes should provide some assistance in interpreting the studies described below and the discussion that follows presentation of results (Chapter 5).

2.2 Historical Context

Picton, et.al. published the first detailed description of auditory evoked responses (AEP) of the brain in 1974 (Picton et al., 1974; Picton and Hillyard, 1974). Years later Thornton (Thornton et al., 1984; Thornton and Newton, 1989) and Jones (Jones, 1994) tested the hypothesis that the amplitude and latency of AEPs reflected the level of consciousness during general anesthesia. While brainstem components (<8 ms) remained unchanged with intravenous agents, mid-latency components (8-40 ms) consistently changed with increasing doses of inhaled and intravenous anesthetics alike. Furthermore, the Nb component of the MLAEP changed with surgical stimulation, providing further validation of MLAEPs as a depth of anesthesia monitor. However, by the early 1990's the accumulated evidence merely correlated mid-latency AEPs with the "arrival of sensory information at primary cortex": higher cognitive processing - perception, as opposed to sensation - could not be assumed (VanHooff et al., 1997). Many researchers in this field speculated that general anesthetics interfere with this very process, and their interest shifted to long-latency AEPs which purportedly reflected cognitive rather than receptive aspects of information processing.

Picton and colleagues also described N1 and P2 long-latency components of the cortical auditory response in their original paper. In the same paper the investigators make brief mention of the effect of physiological sleep on the N1 and P2 components. Collaborating with Näätänen, Picton further characterized the N1-P2 response in awake subjects (Näätänen and Picton, 1987). Only a few years after Picton's landmark 1974 paper, Donchin (Donchin et al., 1983) and colleagues suggested that these components might change with the subject's psychological state. This suggestion, together with a better understanding of the late AEP components, spawned interest in measuring them during physiological sleep and general anesthesia. These lines of research developed

in parallel with characterization of the mismatch negativity (MMN) and P3 long-latency responses. Because these two responses appeared to be independent of attention (specifically the MMN and P3a), they ultimately became important tools in studying disorders of consciousness, namely: coma, sleep, and anesthesia

2.3 ERPs and Depth of Anesthesia

The stated purpose of nearly all early investigations measuring ERPs in anesthetized subjects was to devise a way to objectively assess the level of consciousness or "depth of anesthesia." Physical signs were believed to be unreliable, and the widespread use of muscle relaxants further clouded the clinical picture. The portability of EEG together with the knowledge that auditory stimuli reached cortex, even during deep general anesthesia, led to the first use of evoked potentials to assess consciousness during general anesthesia.

In 1990 Plourde and Picton reported that that the 40 Hz auditory steady state evoked response (ASSR) varied throughout the course of routine surgery in 10 human subjects (Plourde and Picton, 1990). Changes in the level of consciousness were objectively assessed by a button press task, and the ASSR was observed to decrease with decreasing level of consciousness. This work built on Galambos's initial characterization of the ASSR (Galambos, Makeig, and Talmachoff, 1981) and observations regarding its dynamic nature (Galambos and Makeig, 1988). Plourde and Picton's results were consistent with the results of other similar studies on steady state (Hogan, 1987) and transient MLAEPs (Henegan et al., 1987). The authors could not conclude that the ASSR measured consciousness as opposed to arousal or wakefulness.

Persisting in efforts to assess cognitive function during general anesthesia, Plourde and Picton studied the N1 and P3 components in 14 human subjects undergoing routine surgeries (Plourde and Picton, 1991). Their EEG recording system consisted of 3 electrodes: Fz, Cz, and Pz. The P3 was elicited by an "oddball" paradigm with standards (500 Hz, 15 ms) presented at 40 Hz and a single deviant (700 Hz, 75 ms) presented at 10 per minute. Subjects were requested to press a button in response to the deviant - a "hit"; failing to do so counted as a "miss". For "misses" during induction, surgery, and emergence, the amplitudes of the N1 and P3 were indistinguishable from zero.

Interestingly, a few "hits" were observed during emergence, even though resulting responses were also indistinguishable from zero. The authors recognized that the stimulating paradigm was optimized for steady-state responses and therefore not typical. The authors also clearly identified the problem of distinguishing inability or unwillingness to attend from unconsciousness. On the other hand, they confirmed the feasibility of measuring ERPs during surgery and anesthesia. Plourde and Boylan employed a similar study protocol in 8 patients undergoing cardiac surgery and high-dose sufentanil anesthesia (Plourde and Boylan, 1991). While the P3 disappeared post-induction, other components (N1, P2, SW) were preserved. This study highlighted differences in long-latency responses with different anesthetics. The authors concluded that, with some technological tweaking, the P3 response promised to become a useful monitor of consciousness.

Van Hooff and colleagues studied the extent of cortical auditory processing during general anesthesia by focusing on the N1 response (VanHooff et al., 1997). Investigators used a total of 5 scalp electrodes. A classic "oddball" paradigm was presented to 41 patents undergoing cardiac surgery with total intravenous anesthesia. They observed clear differences in the latency and amplitude of P1-N1-P2 complex between the awake and anesthetic states. Deviant responses produced overall higher amplitudes which led the investigators to speculate that MMN and P3a responses might overlap their P1-N1-P2 responses. Importantly, they reported high variability in individual ERPs and that only a minority (30%) showed no ERPs responses. Their study suggested that cortical processing of sensory input is more extensive than previously thought and provided an electrophysiologic basis for the concept of implicit memory during general anesthesia. Finally, especially since anesthetic and patient factors had little effect on their results, these investigators further validated use of ERPs for consciousness monitoring.

As Simpson and colleagues pointed out in their own 2002 report (Simpson et al., 2002), studies on the effects of general anesthesia on long latency auditory-evoked potentials (LLAEPs) were sparse. Recognizing the relevancy of LLAEPs to investigating the anesthetic state as well as the potential usefulness of measuring LLAEPs as a clinical monitor, Simpson et. al. investigated the transition from wakefulness to unconsciousness during a target-controlled infusion (TCI) of propofol. They measured MMN and N1

responses in 21 patients prior to surgery using an "oddball" paradigm consisting of both frequency and duration deviants. EEG data was acquired from 10 standard placed electrodes. The protocol was designed to present only 32 deviants and greater than 200 standards per condition per subject in order to adapt testing to the clinical environment. The MMN disappeared prior to loss of consciousness, defined by the usual criteria of failure to obey commands and loss of lid reflex; whereas the N1 changed from baseline only with loss of consciousness. They confirmed previous findings regarding the usefulness of the N1 response for depth of anesthesia monitoring but concluded that the MMN was insufficiently robust to serve the same purpose. The investigators also noted that over the duration of each epoch ERP waveforms actually became more positive with increasing levels of unconsciousness (i.e. propofol effector site concentration), a finding that suggested the possibility of cortical processing even at deep levels of anesthesia and that deserved further investigation. The authors pointed out the challenge of distinguishing signal from noise with only 32 deviants and acknowledged that reporting results as grand means was dictated by methodology but not ideal. Their study differs from the previously described studies in that, despite the clinical setting, no surgery was performed during the testing period. The Simpson study remains one of the few studies that attempted to measure the MMN response during anesthesia induced unconsciousness (in contrast to sedation only).

Heinke and colleagues studied the differential effects of increasing doses of propofol on the P1, MMN, and ERAN (early right anterior negativity) responses (Heinke et al., 2004). The group hypothesized that responses that were generated in the frontal cortex would disappear prior to those that were generated in the temporal cortex. Eighteen patients were administered propofol by TCI to achieve four different conditions: awake, light sedation, heavy, sedation, and unconsciousness, each defined by target concentrations and behavioral response. Patients were presented with separate ERAN and MMN blocks of stimuli. The ERAN block was based on Koelsch's technique and consisted of sequences of five chords, the third or fifth of which was randomly discordant (25% each). A total of 80 chord deviants were presented to the subject per condition. The MMN block also consisted of a series of five tones, the third or fifth of which was randomly increased in frequency (10%). A total of 40 deviants were presented to the subject per condition. The study employed 18 electrodes placed according to the 10-20 system and predefined

criteria for identifying event-related potentials. The P1 was observed in all four conditions, though reduced in amplitude during unconsciousness; while the ERAN and MMN decreased in amplitude with increasing doses of propofol and disappeared completely during unconsciousness. The investigators observed that the P1 response paralleled typical MLAEPs reported decades earlier. The investigators concluded that propofol does indeed have "different effects on cognitive processes mediated by different cortical structures." Patients were not subjected to surgery during this study.

2.4 ERPs and Recovery From Sedation

The distinction between deep sedation and general anesthesia is arbitrary. Nonetheless a few studies focus on ERP responses during the transition from deep sedation to recovery of consciousness. These studies aim to further investigate cerebral auditory processing, characterize the ERP responses themselves, identify electrophysiologic markers of adequate sedation or recovery from sedation, or clarify the pharmacodynamics of particular drugs. Propofol became widely available around the year 2000, and it quickly became the preferred drug for ICU and procedural sedation. Therefore, in most of these reports, ERP responses are studied in subjects sedated with propofol.

Yppärilä and colleagues studied the auditory event-related responses of 29 patients recovering from cardiac surgery and sedated with propofol in the ICU setting (Yppärilä et al., 2002). ERPs of interest included the N100, MMN, and P300a. Sedation level was assessed by behavioral criteria using the Ramsay score (RS). Three recordings were obtained: baseline (day before surgery), deep sedation (RS 6, immediately after surgery), and moderate sedation (RS 4, during "weaning"). EEG data was acquired using only four electrodes: Fz, Cz, C3, C4. The investigators used a typical "oddball" paradigm with a total of 700 stimuli consisting of 85% standards and 15% frequency deviants. During deep sedation patient responses varied but could be grouped into three categories. In the "no response" group (6/26) no responses were detectable. In the "detection" group (9/26) only an N100 was observed. In the "arousal" (11/26) group both an N100 and P300a was observed. The authors do not comment specifically on the MMN in these three groups. But summarized data showed that the MMN amplitude was significantly different between sedation and baseline but not significantly different between moderate and deep sedation.

Without elaboration the authors noted that a P300a was more likely observed in deep sedation (11/26) than in the baseline condition (7/26). The investigators concluded that N100, MMN, and P300a are delayed in latency and reduced in amplitude during sedation and that propofol sedation causes a sensory memory function deficit.

Koelsch, Heinke, Sammler, and Olthoff investigated auditory processing during propofol sedation in 19 healthy volunteers (Koelsch et al., 2006). Measurements were obtained in three conditions: awake, deep sedation, and recovery. EEG data were acquired using an 18-electrode montage conforming to the 10-20 system. Propofol was delivered by TCI to achieve deep sedation which was verified by behavioral criteria (MOAAS 2 – 3), BIS (mean 68), and a timbre detection task. Similar to this group's previous study, study subjects were presented both MMN and ERAN blocks. The MMN block consisted of 80% standards and 20% mixed deviants (frequency, timbre, omission); however, only results for frequency deviants were reported. Approximately 300 deviants were presented. The ERAN block was similar to the group's previous study. Prior to the recovery phase, subjects were administered additional propofol to produce unconsciousness. The infusion was then discontinued, and subjects were allowed to recover. No measurements were obtained during this brief period of unconsciousness. The MMN was detectable during all three conditions, although it was significantly reduced in amplitude during deep sedation. In contrast, the ERAN was not detectable during deep sedation. Interestingly, a P3a response was not present during the recovery period when BIS values were higher and propofol levels lower than during sedation. The investigators concluded that during propofol sedation auditory memory processes are intact, music (and language) syntactic processing is abolished, and recovery of attention related processes is delayed.

A study led by Haenggi attempted to use ERPs to define adequate sedation in an effort to avoid the side-effects and risks of sedative medications (Haenggi et al., 2004). Ten healthy subjects were sedated with propofol, remifentanil, or a combination of the two. Drugs were administered by TCI to staged behavioral endpoints. At each stage a "habituation" and oddball auditory paradigm was administered, and N100 and MMN responses were measured from a single electrode (Cz). Investigators used a low pass filter of 8 Hz in order to remove corticothalamic oscillations. N100 amplitudes decreased with increasing levels

of sedation. The majority of patients did not show an N100 response at deep levels of sedation (RS 5 or 6). Neither habituation (ratio of first N100 response to second N100 response in the "habituation" paradigm) nor MMN could discriminate between sedation levels. Remifentanil did not affect the ERPs at various target concentrations. The authors conclude that measuring the N100 can effectively guide the level sedation when propofol is used in a way that avoids loss of consciousness. Although the aims of this study were different, its conclusions were similar to those of Simpson (2002).

In a recent study investigators attempted to use the MMN response to predict awakening after discontinuation of sedation in ICU patients (Azabou et al., 2018). Azabou and colleagues studied 43 intubated and ventilated patients who required sedation. The sample population consisted of critically ill patients with a wide variety of underlying medical problems but excluded those with recent cardiac arrest, brain-death, and neuropathy. In this study the majority of patients (>80%) were sedated with midazolam and sufentanil. Investigators used a simple two electrode system (Fz, Cz) and exposed subjects to a classic passive oddball paradigm implemented in crossover design. Data points consisted of averaged responses based on 200 deviants. ERP responses for 13 patients who did not awaken were visually distinct from the 30 patient who did awaken. As shown by non-parametric statistical analysis, individual patient MMN amplitudes were greater (more negative) in the awake group than the non-awake group. Effects appeared related both to the cumulative midazolam and the severity of illness. Authors of this pilot study concluded that the MMN response predicts awakening in deeply sedated critically ill patients. The authors also state that their results and conclusions are consistent with the ability of the MMN to predict recovery in vegetative states.

2.5 ERPs as Biomarkers of Post-operative Cognitive Dysfunction

Approximately 15-20% of all patients who undergo general anesthesia experience delirium or postoperative cognitive dysfunction (POCD). Whereas the effects of anesthetic drugs were once thought to be transient and reversible, biologically plausible models of persistent cognitive changes now

exist (Hemmings et al., 2019). The consequences of POCD include increased costs to the health care system and an unknown contribution to long term cognitive decline (dementia). Considerable resources are currently allocated to prevention and early detection of POCD, as well as quantification of risk of long-term cognitive deficit. Several large trials, ENGAGES for example, investigated the relationship between the duration of burst-suppression on the EEG during general anesthesia and various cognitive outcomes (Wildes et al., 2019). The ENGAGES trial yielded negative results; despite methodological strengths and weaknesses, results suggest that resting EEG may have limitations. Since ERPs have an established role in differentiating coma-related disorders of consciousness, they might equally identify subtle, subclinical deficits that underlie POCD.

Holečková and colleagues studied auditory ERPs in 52 patients who underwent spine surgery (Holečková et al., 2018). Patients were subdivided into two groups based on anesthetic technique – inhaled (IA) versus total intravenous anesthesia (TIVA). Preoperatively, and day 1, 6, and 42 postoperatively, they measured the N1, P3a, and P3b response using an "oddball" paradigm consisting of 3 blocks of 400 stimuli (80% standards, 20% frequency deviants). EEG analysis was based on scalp recordings at 2 electrodes, Fz and Pz. The study revealed a significant increase in N1 latency response in IA compared to TIVA on day one. Amplitudes for P3a and P3b were all reduced compared to preoperative measurements, but no differences between IA and TIVA were noted. The reduction in the P3b amplitude normalized by day 6, but reduction in the P3a amplitude persisted to day 42. These results are difficult to interpret because of confounding factors of analgesic therapy and pain. Whether the identified ERP abnormalities correspond to behavioral outcomes is also open to question.

2.6 Anesthetic drugs as probes in ERP studies

Perturbational approaches to exploring consciousness have distinct advantages over approaches based on the resting EEG (Boly et al., 2012). Propofol, arguably the most studied anesthetic agent in recent times, affects cortical dynamics in predicable ways. Therefore, analogous to TMS, it can perturb an experimental model in order to induce observable changes in and draw conclusions about

the underlying brain state. Unlike TMS, propofol is relatively easy to administer and requires no additional equipment beyond the basic ERP setup.

Blain-Moraes and colleagues piloted use of propofol to predict transition of individuals from the unresponsive wakefulness state (UWS) to the minimally conscious state (Blain-Moraes et al., 2016). In this study of one patient investigators compared ERPs and EEG connectivity measures at baseline, during propofol infusion (TCI 2 mcg/mL), and during recovery. Propofol altered all electrophysiologic measures in the UWS patient similarly to healthy individuals: loss of ERP responses, decrease in high-frequency power, anteriorization of alpha, and decrease of fronto-parietal connectivity. The patient subsequently made a significant clinical recovery. The authors speculate that observation of the typical cortical changes associated with propofol indicated sufficient brain substrate for recovery from the traumatic coma state. Subsequently, a larger clinical trial was planned.

Zhang and colleagues used propofol to further investigate the neurobiology of the MMN response in humans (Zhang et al., 2018). Investigators speculated that deviant stimuli would engage long distance cortical connections, which would be blocked by propofol; whereas standard stimuli would only engage short distance connections which would not be altered by propofol. EEG was recorded during an MMN paradigm in 25 healthy subjects under conditions of wakefulness and anesthesia. Source analysis identified connected brain regions involved in the processing of the stimuli. In the awake state, deviant stimuli induced a larger number of connections than standard stimuli. Long-distance connections accounted for the majority of this difference. In the anesthetized state, standards and deviants induced the same number and kind of connections. However, the number of long-distance connections were markedly reduced during general anesthesia compared to the awake state. The authors concluded that the cortical regions corresponding to these differences contribute to the generation of the MMN and that MMN activates a wide fronto-temporo-parietal network.

A relatively recent study by Nourski and colleagues spans dual purposes of attempting to understand anesthesia-induced unconsciousness and using propofol as a probe to further elucidate auditory predictive coding (Nourski et al., 2018). Their approach is significantly different from previously

referenced studies: first, they used strategically placed implanted electrode arrays (electrocorticography or ECoG); and second, they used the local-global paradigm devised by Beckinschtein (Bekinschtein et al., 2009)[1]. Their subjects included six patients with refractory epilepsy. ECoG recordings were obtained during three states: awake, sedated, and unconscious, which was defined as unresponsiveness to verbal command. No surgery was performed during recordings. Effects were defined as differences between deviant and standard and determined by cluster permutation tests, and differences among states were confirmed by hierarchical regression techniques. Reconstruction of anatomical locations was accomplished with standard imaging software. The primary finding in this study was that in the unconscious state, local deviant effects persisted in primary auditory cortex (but not other cortex), while global deviant effects dissipated during sedation and were absent in unconsciousness. These findings are remarkable for several reasons. They confirm that primary auditory cortex is relatively resistant to anesthetic drugs and that loss of higher cortical function occurs prior to loss of consciousness during drug administration, which was demonstrated by Simpson in one of the very first MMN anesthesia studies. In practical terms, absence of global deviant effects is not a biomarker of unconsciousness, while absence of local deviant effects in non-auditory cortex might well be a marker. The study is also interesting because the investigators draw conclusions exactly opposite to those of Uhrig and colleagues who also used a local-global paradigm and fMRI (Uhrig et al., 2016). In multiple ways, this study highlights the usefulness of ERP for investigating consciousness.

[1]The local-global paradigm is a variant of the classical auditory oddball paradigm. It has two levels of regularity. The building block is a five tone sequence in which the first four tones do not vary. The fifth tone may be the same as the previous four (standard) or different (deviant) thereby generating local variation. The block, whether standard or deviant, is repeated multiple times with random interspersing of the other kind of block, thus giving rise to global variation. Blocks can be assembled to produce four kinds of trials: local standard/global standard, local deviant/global standard, local standard/global deviant, local deviant/global deviant.

Chapter 3

Methods

3.1 Study Design

This study was an observational study. No intervention, other than an EEG recording itself, was undertaken. When possible, two sets of EEG data were collected in each participant: a "control" data set obtained during the awake state; and a" test" data set obtained during general anesthesia and surgery. Data were analyzed retrospectively for a specific event-related response (i.e. MMN) using a variety of statistical techniques.

This study, inclusive of multiple amendments, was approved by the Hamilton Integrated Research Ethics Board (Project 4861).

3.2 Study Population

This study targeted patients undergoing long (> 3 hours) surgeries with general anesthesia. This time requirement allowed the study team to obtain multiple EEG measurements during the same surgery. Eligibility was determined by the following criteria and assessed by the physician member of the study team. The exclusion criteria attempted to minimize any possible confounding factors that might have an impact on the EEG recording.

3.2.1 Inclusion and Exclusion Criteria

Inclusion Criteria:

- Age 40 – 70

- Scheduled surgical procedure (elective), which might include oncologic; chest, urologic, abdominal wall, or bowel reconstruction; hepatobiliary; and vascular surgeries.
- Anesthetic type: general anesthesia
- Duration of surgery: > 3 hours.
- ASA 1, ASA 2, or ASA 3, as defined by American Society of Anesthesiologists (ASA) Physical Status Classification System (Appendix C) with adequately treated and stable systemic disease

Exclusion Criteria:

- History of anesthetic related problems, such as airway or blood pressure management
- Anticipated airway management problems
- Impaired hearing
- Intracranial pathology, at present or in past, including traumatic brain injury
- Concurrent maintenance opioid therapy
- Substance abuse, ethanol, opioids, or amphetamines
- Neurodegenerative disease, formally diagnosed
- Seizure disorder, requiring treatment

3.2.2 Recruitment and Consent

Potential subjects were identified at the time of surgical consultation when consent to proceed with surgical intervention was obtained. At that time patients were approached by the surgeon or office assistant for consent to be contacted by a member of the study team. Consenting patients were then contacted by telephone for the purpose of obtaining consent to participate in the actual study. Office staff who made a referral were offered a $10 gift card (e.g., Starbucks or Tim Hortons) for every eligible patient. Pending consent to participate, arrangements were made for performing the EEGs as outlined below.

3.2.3 Sample Size

In a study of this nature an appropriate sample size cannot be quantitatively determined. The initial goal was to enroll 10 patients, which is a typical number for event-related potential (ERP) studies. The small sample size and relative overall difficulty recruiting patients, prohibited setting requirements for specific demographics.

3.3 Anesthetic Care

Patients received standard anesthetic care. Standard CAS monitors were applied, including a peripheral nerve stimulator. The choice of anesthetic drugs and doses were determined by the attending anesthesiologist. Maintenance consisted of inhaled agent (of choice) to achieve a minimum alveolar concentration (MAC) of 0.7 or greater. Additional opioids, muscle relaxants, and adjuvants were administered at the discretion of the attending anesthesiologist. Prior to emergence, long-duration opioid (morphine or hydromorphone) – if applicable – along with antiemetic medication and neuromuscular blockade reversal drugs were administered. Routine postanesthetic care was provided by the healthcare team.

3.4 Data Acquisition

Control recordings were made at the time of a preoperative visit to Hamilton Health Sciences (HHSC) or, alternatively at the Language, Brain, Memory Lab at McMaster University. Test recordings were made in one of the hospital's operating rooms after induction of general anesthesia and surgical incision. Typically a gap of several days to 2 weeks separated the two recordings. Control sessions consisted of two presentations of the auditory paradigm. During surgery, the same auditory paradigm was presented two to 10 times, depending on the duration of surgery; recording was terminated prior to wound closure. All recordings were obtained by trained personnel.

An appropriately sized BioSemi 64-channel EEG cap was applied to each participant. EEG data were acquired using the BioSemi ActiveTwo^{TM} EEG system (based on the international 10/20 system). This active system utilizes 2

additional electrodes incorporated into the cap. Five "external" electrodes were also applied directly to the patients skin. These included nasion, right and left mastoid, and vertical and horizontal (left) eye electrodes. Standard conduction gel was used to achieve contact between scalp or skin and the electrodes. Real time data was sampled at 512Hz using a 0.1–100 Hz filter.

During all testing, participants wore earphones (Cortech, SD-AV-EAER1), through which a multi-deviant auditory oddball paradigm (Todd et al., 2008) was presented. A digital audio file, incorporating features of the paradigm, was prepared using Presentation®(Neurobehavioral Systems) software and played-back on a dedicated computer. The resulting audio output, along with stimulus markers, was multiplexed to the EEG recording computer in order to minimize any delay between the auditory stimulus and brain response. The paradigm consisted of 82% standards, and three deviants forming a total of 18% of the stimuli. The inter-stimulus interval was 500 ms. Standards tones were 1000 Hz presented for 50 ms at 80 dB sound pressure level (SPL). Each of the deviant tones were identical to the standard in all but one feature: frequency deviant, 1200 Hz; duration deviant, 150 ms; and intensity deviant, 90 dB SPL. Therefore, a single presentation or "block" consisted of 2400 items: 1968 standards, 144 frequency deviants., 144 duration deviants, and 144 intensity deviants.

3.5 Data Analysis

Raw data was preprocessed using EEGLAB (Delorme and Makeig, 2004). On import, data were re-referenced to mastoids (average of left and right). Next, channel names were assigned using a standard BioSemi assignments, and external electrode channels were removed. Data were filtered using a highpass of 0.1 Hz and a lowpass of 30 Hz. A visual inspection of data was then performed, with the goal of removing gross artifacts. Control data was subjected to ICA (Infomax) in order to identify and remove eye blinks. All data was then passed through the EEGLAB "Clean Raw Data" toolbox (Miyakoshi, 2020) to identify bad electrodes, defined as electrodes that failed to correlate with neighboring electrodes more than 40% of the time. Bad electrodes were then interpolated.

3.6 Statistical Analysis

Analyses were performed at the epoch level with the goal of identifying any statistically significant deviant-related negativity using MNE-Python (Gramfort et al., 2013). Preprocessed data files (each representing one block) were epoched using the markers attached to the raw data files by Presentation®. Time contiguous blocks that contained less than 1000 standards or 100 deviants were concatenated and re-inspected prior to further analysis. Epochs from each file were visualized by averaging amplitudes from FCz, Fz, and Cz for standards and each deviant. Means and standard deviations (over epochs) were plotted over the time interval -100 ms to 600 ms. This plot revealed which deviant produced the greatest response and whether the response differed significantly from zero microvolts. Additionally, evoked responses (averaged over the block's epochs) were plotted over the same time interval. The deviant showing the most significant negative deviation was then plotted with its corresponding standard and difference wave. Next, using the most prominent deviant, targeted t-tests were performed across two time intervals, 200-250 ms and 250-300 ms, for each of FCz, Fz, and Cz. No error-rate corrections were made. Finally, again using the epochs with the most significant negative deviation, permutation cluster-based analyses were performed (Maris and Oostenveld, 2007; Smith and Nichols, 2009). In order to compare results from standard statistical tests and machine learning, multivariate pattern analysis (MVPA) was also performed (King et al., 2018).

3.6.1 ERP Images

ERP images combine data visualization and statistical analysis (Gramfort, Keriven, and Clerc, 2010; Gramfort et al., 2013). The ERP image consists of epochs depicted as lines and stacked vertically. Each epoch is aligned along the same time scale. Each time point in the epoch is color-coded for amplitude. On a typical computer display hundreds of epochs can be displayed in a relatively small format. Color-coding of amplitude allows patterns to emerge, often seen as vertical bands, that represent significant positive or negative deflections in the ERP. Thus, in a single glance, the viewer can assess whether the ERP of interest is present in a majority of epochs. The average ERP at each time point can be displayed below the image along with 95% confidence limits, which

together provide reliable information about when and to what extent the average ERP differed from zero microvolts (see 4.1).

3.6.2 Cluster-based Analyses

Cluster-based analysis aims to reliably differentiate two conditions (Maris and Oostenveld, 2007). Analysis is designed to obviate the multiple comparison problem which invariably accompanies analysis of multidimensional EEG data. Assuming the two time series (i.e. conditions) arise from the same underlying probability distribution (null hypothesis), a t-test is performed on each time point with a random selection of epochs from each condition. Comparisons with t-values greater than an arbitrarily chosen threshold are amassed into a "cluster." If the t-value of the next time point also exceeds the threshold, its t-value is added to the cluster; otherwise the comparisons continue until another comparison exceeds the threshold and a new cluster is formed. The total t-values of the individual time points in the cluster(s) are stored. A histogram representing the cluster permutations is constructed. Finally, the clustering procedure is performed on the two observed conditions. If the probability of the observed total t-value is less than 0.05, the two conditions are assumed different. Thus, a single inference is drawn with regard to the observation and the constructed cluster permutation distribution.

Results of cluster-based analysis can be visualized in different ways. When time-based, analysis is performed electrode by electrode. The time course of activity at each electrode can be depicted as a line; each time point can be color-coded for the probability associated with the cluster permutation t-test. Then the timelines of different electrodes can be stacked and grouped by topography - anterior, central, parietal, e.g. - such that blocks of color represent times and topographies where results were significant (see 4.3). Alternatively, clusters can be defined in terms of adjacency in both space and time. In this case, the global field power of all electrodes is plotted for each time point; and significant clusters, identified as described above, are displayed by annotating the plot at the corresponding time interval (see 4.4). The latter approach is readily adapted to comparison of multiple conditions. Cluster-based visualizations and statistics used in this study were implemented in MNE-Python (Gramfort et al., 2013).

3.6.3 Multivarvariate Pattern Analysis

Multivariate pattern analysis (MVPA) is a machine learning technique applied to EEG data. (King et al., 2018). In this regard analysis incorporates the typical steps of data transformation, model fitting, and prediction. When applied to EEG data, MVPA amounts to deriving a spatial filter at every time point (from a subset of train data) and then applying that filter to (test) data in order to determine whether it can distinguish one condition from another. The train-test data split was accomplished using simple 5-way cross-validation. The various folds were not shuffled or stratified, and the cross-validation process was not repeated. This study employed a logistic regression classifier with hyperparameters optimized for imbalanced data sets. Linear classifiers have the advantage of permitting back calculation and visualization of spatial filters. Prediction accuracy was assessed by ROC-AUC at every time point; and 95% confidence limits were derived from the cross-validation. Results of the analysis were visualized by plotting accuracy versus time (see 4.5). Accuracies with confidence interval greater than 50% were considered significant. Empirical testing showed that this choice of methods for cross-validation and fitting resulted in maximal accuracies with minimal computation time. The MNE-Python implementation used in this study borrowed heavily from ScikitLearn (Pedregosa et al., 2011).

Chapter 4

Results

4.1 Collected data

Data collection as specified in Chapter 3 was completed on five patients. In another five patients, control data was not collected due to scheduling of surgery on short notice and inability to mobilize the study team. One of these patients was recruited and consented, but due to intraoperative factors (discussed below) data of sufficient quality was not recorded. Patient demographics are described in Table 4.1. A summary of the data collection is described in Table 4.2.

TABLE 4.1: Patient Demographics

Patient	Age	Sex	Diagnosis	Surgery Type
1	M	56	ventral hernia	abdominal wall repair
2	F	70	colon Ca	bowel resection
3	F	53	colon Ca	resection
4	F	68	colon Ca	bowel resection
5	F	52	breast Ca	breast reconstruction
6	F	51	breast Ca	breast reconstruction
7	F	62	breast Ca	breast reconstruction
8	F	44	breast Ca	breast reconstruction
9	F	53	breast Ca	breast reconstruction
10	M	60	sarcoma	muscle resection & reconstruction

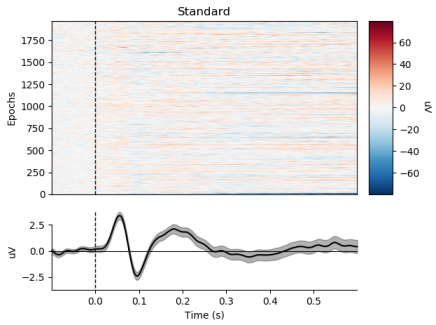
M male; F female; Ca carcinoma

TABLE 4.2: Acquired Data Blocks

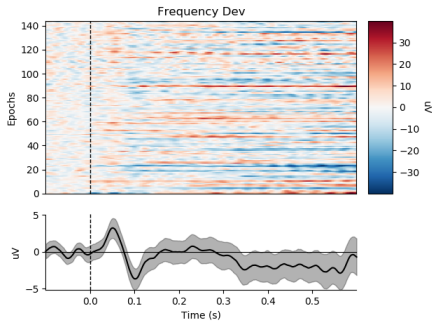
Patient	**Control**		**Test**	
	Recorded	Analyzed	Recorded	Analyzed
1	2	2	9	6
2	2	2	2	2
3	0	0	4	3
4	2	2	5	3
5	2	2	6	3
6	0	0	0	0
7	2	2	3	3
8	2	2	10	7
9	0	0	5	3
10	0	0	8	6

4.2 Control Data

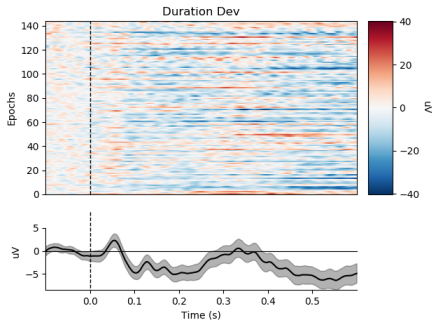
Each of the five patients on whom control recordings were obtained provided two blocks which were acquired sequentially. In all ten recordings an MMN response could be identified on visual inspection. Inspection of the epoch image plots (see Figure 4.1) revealed that the duration deviant produced the most deviant related negativity. Targeted t-test statistics, without correction, were significant in the 200-250 ms range for the duration deviant in all recordings. Time-referenced cluster-based statistics, which compared standard to duration deviant, were significant in all blocks, though in one block (patient 4, block 2) the number of identified clusters was very small. Sensor-time referenced clustered-based statistics, once again comparing standards to duration deviants, were significant in all blocks except one (patient 7, block 1). Multivariate pattern analysis (MVPA) identified a difference between standards and duration deviants in all patients with an accuracy of 0.643 - 0.761 ROC-AUC (area under the receiver operator curve). Peak accuracy fell in the expected 170-240 ms time interval and was significantly different from chance (50%) at a p-value of 0.05 in all blocks. Equal covariance between classes was verified using the principal component method of Blankertz (Blankertz et al., 2011). Taken together, these results demonstrate that the methods used in this study could reliably distinguish standard from deviant in the evoked EEG.



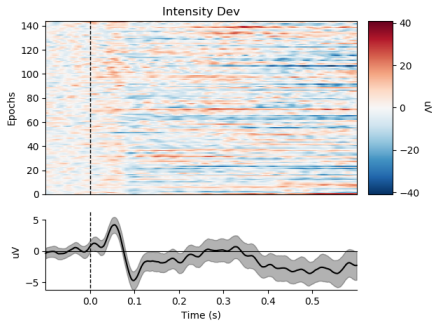
(A) Standard epochs



(B) Frequency deviant epochs



(C) Duration epochs



(D) Intensity deviant epochs

FIGURE 4.1: Example of control epoch images "stacked" on mean amplitude with 95% CI. Figure (c) shows that duration deviants are statistically distinguishable from zero in the time interval around 200ms.

(A) Time series for all conditions

(B) Time series for duration deviant

FIGURE 4.2: Example of control time series averaged over all epochs in a single control block. Figure (b) shows a visually distinct deviant associated negativity in the time interval around 200 ms.

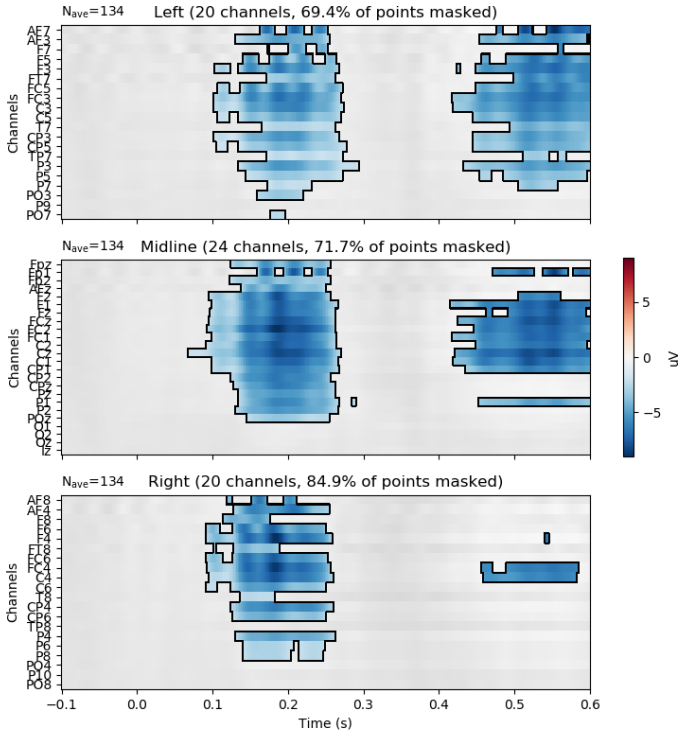


FIGURE 4.3: Visualization of time clusters. Blue colored blocks represent statistically significant clusters. Axes indicate where these clusters are located in sensor-time space. The most intense blue is seen in central electrodes in the time interval around 200ms.

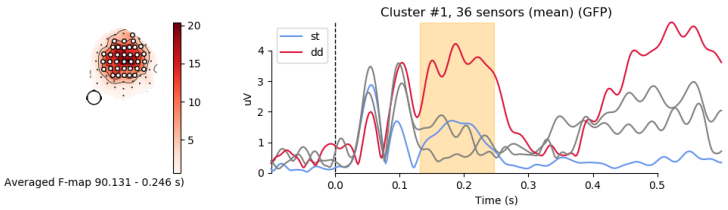


FIGURE 4.4: Visualization of sensor-time clusters. Significant clusters are indicated by the highest GFP in the time interval delimited by the orange box. Analysis reveals significant clusters related to the duration deviant in the time interval around 200 ms.

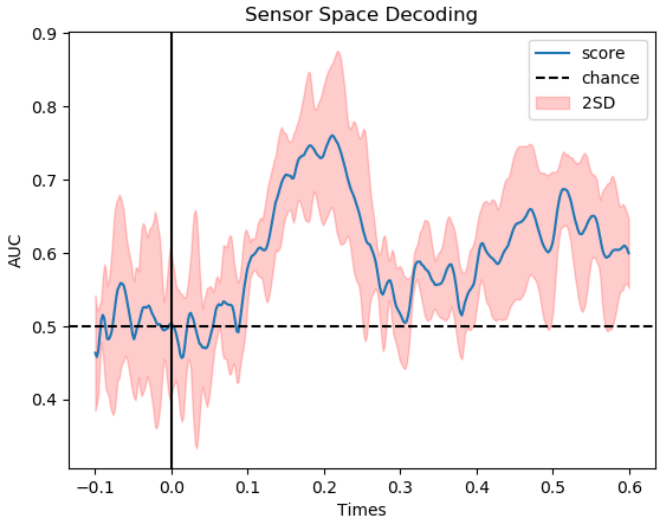


FIGURE 4.5: MVPA results for single control block. Results show that the classifier can reliably distinguish standards from deviants in the interval around 200ms.

4.3 Test Data

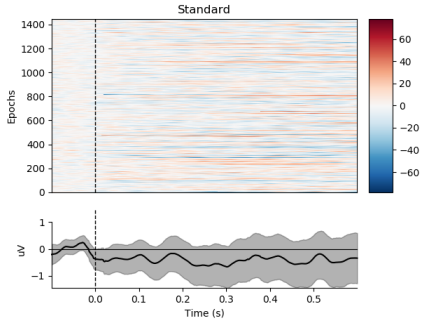
The amount of recorded data depended on the duration of surgery, the use of electrocautery, and presence of electromagnetic interference originating from equipment in the operating room. Of the 52 blocks of acquired data, 35 were suitable for further analysis. Table 4.3 shows the distribution of analyzed blocks by patient. The 35 blocks varied in duration and number of epochs of interest due to removal of artifacts, most of which were caused by the surgeon's use of electrocautery. The mean number of standard epochs in the analyzed blocks was 1541 (interquartile range 1386 - 1702). The mean number of duration deviant epochs in the analyzed blocks was 111 (interquartile range 99 - 127).

TABLE 4.3: Number of Test Blocks Per Patient

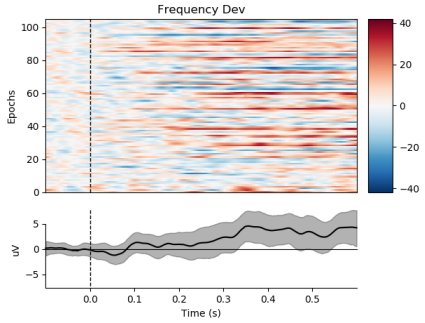
Patient	Blocks
1	5
2	2
3	2
4	3
5	3
7	3
8	7
9	3
10	7

Visual inspection of the epoch images showed considerable overlap of 95% confidence intervals around the mean amplitudes and zero microvolts (Figure 4.6). Therefore the observed deviant related activity could not reliably be labeled "negative," which is characteristic of the mismatch response. Targeted t-tests were not significant in 29 blocks and were significant in six blocks. These six blocks were acquired in five different patients. Only two of the six blocks showed negative event-related potentials. Spatio-temporal cluster based analyses were uniformly negative for all observed deviant related negativity (Figure 4.8). With 95% confidence intervals overlapping the chance level of 50% for 2-class classification, MVPA classification accuracies were consistently statistically indistinguishable from chance or less than 60%

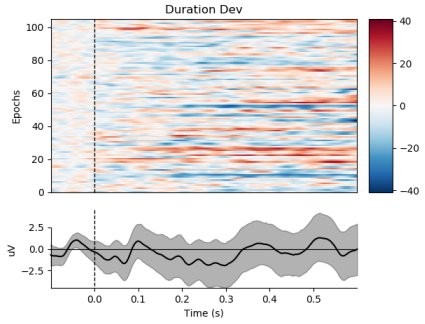
(Figure 4.9). Taken together, these results demonstrate that deviants were indistinguishable from standards during general anesthesia.



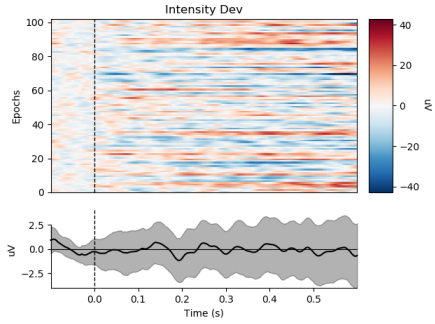
(A) Standard epochs



(B) Frequency deviant epochs

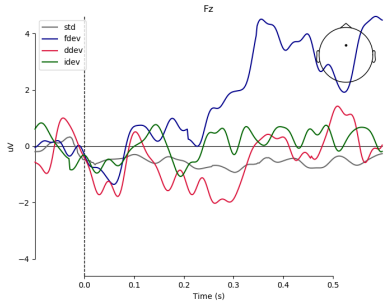


(C) Duration epochs

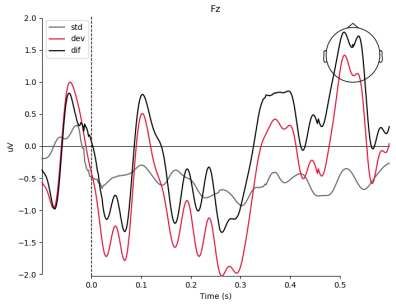


(D) Intensity deviant epochs

FIGURE 4.6: Example of test epoch images "stacked" on mean amplitude with 95% CI. Confidence intervals for all deviants encompass zero. Deviant related activity can not be statistically distinguished from zero and, therefore, cannot be reliably labeled "negative."



(A) Time series for all conditions



(B) Time series for duration deviant

FIGURE 4.7: Example of test time series averaged over all epochs in a single control block. Standard and deviant time series are not visually distinct in the time interval of interest, around 200ms.

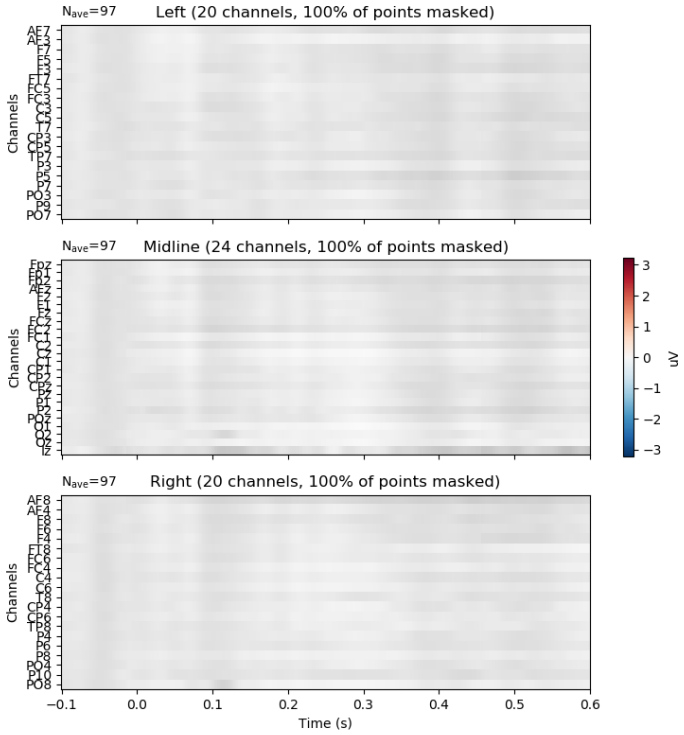


FIGURE 4.8: Visualization of time clusters in one test block. The lack of any blue blocks in the graphic indicates failure to identify any clusters encompassing deviant-related negativity.

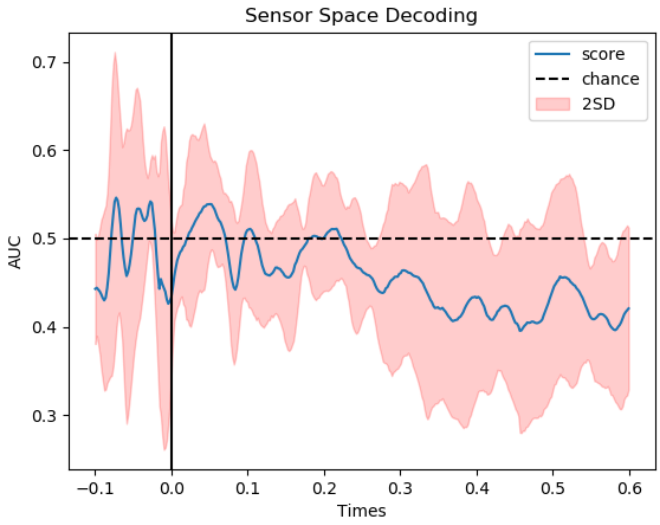


FIGURE 4.9: MVPA results for single test block. Confidence intervals for accuracy encompass the chance level of 50% at all time points. The classifier could not reliably distinguish standards from deviants.

Chapter 5

Discussion

This study addressed two questions: one, could a an MMN response be detected during routine general anesthesia and surgery; and two, could the presence (or absence) of the MMN response vary over time depending on the state of the patient. Results indicate that an MMN response could not be detected during routine general anesthesia and surgery. The significance of these results - with regard to past ERP studies, auditory cortical processing, and nature of anesthesia induced unconsciousness - is discussed below. Following this discussion, attention shifts to the several important ways in which this study differs from previous similar studies. These differences are presented in the context of study strengths and weaknesses.

5.1 A negative result in context

Inability to demonstrate an MMN response during general anesthesia is consistent with previous studies. The Simpson (Simpson et al., 2002) and Heinke (Heinke et al., 2004) studies failed to demonstrate an MMN during general anesthesia. The sedation studies of Yppärlä (Yppärilä et al., 2002), Koelsch (Koelsch et al., 2006), and Haenggi (Haenggi et al., 2004) demonstrate a dose-dependent effect of anesthetic drugs on the MMN which supports the notion that the higher doses used in general anesthesia might ablate the response. Finally, studies examining the P300a or ERAN during administration of anesthetic drugs (Plourde (Plourde and Picton, 1991), Heinke, Yppärlä, and Koelsch) failed to demonstrate persistence of these long-latency ERPs. These studies support the concept that higher cortical functions are impaired by anesthetic drugs and, by implication, that the MMN would be equally diminished. All of these studies used an odd-ball auditory paradigm, relatively

simple EEG setups, and conventional univariate statistics. Only the Plourde and Van Hoof (VanHooff et al., 1997) studies were conducted during surgery, and neither study measured the MMN response. Despite the methodological differences among all these studies, the summed evidence aligns with results of the current study.

More recent studies investigate the neurobiology of cortical processing of auditory stimuli, in general , and novel stimuli, specifically, during exposure to anesthetic drugs. Both the Zhang (Zhang et al., 2019) and Nourski (Nourski et al., 2018) studies, though very different, suggest that general anesthetics have little effect on primary auditory cortex and mainly affect cortical network dynamics. This conclusion is confirmed by other recent studies (Banks et al., 2018; Krom et al., 2020) which do not incorporate an odd-ball paradigm into their methods. In comparison to the older studies cited above, these studies use source modeling and implanted electrode arrays. Nonetheless, they suggest that an MMN response which incorporates a hierarchy cortical responses, cannot be elicited in an anesthetized patient.

Long-latency ERPs figure prominently into currently prevalent theories of consciousness, namely predictive coding (Friston, 2005) and global neuronal workplace (GNW) theories (Mashour et al., 2020). In the case of predictive coding, activation of primary sensory cortex coincides with a hierarchy of processes: feedback of higher cortical predictions, feedforward prediction error propagation, modulating estimates of significance of the error (precision), and subsequent updating of the higher cortex. Proponents of predictive coding recast the MMN response as a failure to suppress prediction error, a process that "rests on plasticity in backward and lateral connections" (Friston, 2005). In the case of GNW, long-latency ERPs represent evidence of "ignition", or broadcast, to higher cortical areas which amplify and sustain sensory input through recurrent activity. Proponents of the GNW theory cite the P300b as evidence of ignition: with its characteristic timing and requirement for attention, this response represents the threshold where stimuli become globally accessible. This study and other similar studies (see Chapter 2) show that general anesthetics suppress long-latency ERPs and, by implication, disrupt functional connectivity. While the relationship of disrupted cortical connectivity to anesthesia-induced unconsciousness is still a matter of investigation and the results of the current study have no direct bearing on this

matter, these results are nonetheless consistent with predominant themes in consciousness research.

Finally, these results validate an important aspect of contemporary anesthesia practice. Ongoing arguments about the choice of brain monitoring technologies and their effectiveness - particularly with regard to preventing intraoperative awareness - has led to a plethora of studies (Messina et al., 2016). One of the most influential studies to date (Avidan et al., 2011) demonstrated that maintaining an end-tidal anesthetic concentration (ETAC) of 0.7 MAC of any inhaled agent reduces the probability of awareness to less than 0.4%. Maintaining this concentration of inhaled agent was incorporated into the methodology of the current study. No patient showed an MMN during general anesthesia. One can only conclude that this concentration of inhaled agent disrupts the brain's perceptual processing and that this disruption contributes to lack of awareness. Thus, this study provides a neurophysiological basis for an important clinical finding.

5.2 ERPs in the operating room environment

Since previous studies failed to demonstrate an MMN during general anesthesia, and the effects of surgical stimulation could only enhance CNS activity, it seemed reasonable to determine whether an MMN could be identified under general anesthesia during surgery. The aim of the study design was to remain practical and not substantially alter the care of the patient. Thus, participating anesthesiologists were required to use an inhaled agent in a concentration consistent with unconsciousness, but were otherwise unhampered in individualizing pharmacologic management. Accordingly patients did receive, in varying amounts, benzodiazepines and opioids which undoubtedly affected the state of the CNS. This result was unavoidable, given the parameters of the study. To control the anesthetic to any greater degree would lead to deviations from standard of care that would obviate research ethics board approval or deter patients from participating. Moreover, the more prescribed the anesthetic regimen, the less generalizable the results. Likewise, nociceptive input could not be controlled in a rigorous way or even quantitated. As stated above (in Chapter 1) the anesthesiologist's primary role is to mitigate the nociceptive response. Methods to quantitate the nociceptive state do exist - pupillometry, skin conductance, e.g. - and follow up studies

should perhaps incorporate these methods into their protocols. Nonetheless, considering the anesthesiologist's efforts to mitigate the nociceptive response and the variable nature and intensity of surgical stimulation, questions arise whether the resulting effects would in any circumstance be sufficient to trigger an MMN response. What can be said is this: in ordinary patients, undergoing ordinary surgeries with typical anesthetic techniques, an MMN was not observed.

The operating room (OR) is a challenging place to conduct research. Electrocautery was the leading cause of data loss. It is used in almost every surgery, and some surgeons use electrocautery throughout the entire operation. Surgeons use two different types of electrocautery - unipolar, and bipolar - each causing different kinds of artifacts (see Figure 5.1). Despite efforts, recovery of the underlying signal was not possible. Other OR instrumentation also likely contributed to signal contamination, but the 30 Hz low pass filter effectively eliminated most of it. Another source of signal contamination related to the OR environment includes passive movement of the head (by the surgeon) and involuntary movement of the patient. The latter was minimized, but not completely eliminated, by the use of muscle relaxants. Tiny movements of the neck, head and eyes were still possible. Whether the 30 Hz low pass filter eliminated artifacts due to all muscle activity is unknown. Patients frequently become diaphoretic during general anesthesia and surgery, and this causes a potential problem of "electrode bleeding." In fact, patient no. 6 sweated so profusely, that about 15 electrode locations were rendered useless; consequently, the study was discarded. Potentially, the audio stream reaching the patient was obscured or contaminated by operating room ambient noise. The mean noise level in an OR is 60-65 dB, but levels can intermittently reach 100 dB (Giv et al., 2017). The "noise" is mix of monitoring alarms, powered instruments, conversation, and music. Lastly, and somewhat related, when the patient is unconsciousness there is no way to confirm that they are actually receiving the intended audio stream. The unconscious patient cannot respond verbally, and an N1 response is not uniformly seen under general anesthesia.

(A) Electrocautery artifact (B) Unknown source

FIGURE 5.1: Examples of two types of artifact due to a electromagnetic source. The source (A) was clearly related to unipolar cautery, whereas source of (B) was never found with certainty but likely due to bipolar cautery.

5.3 Serial recordings

Recent research into using ERPs to predict emergence from coma suggests that in disorders of consciousness, an MMN response may be present only transiently (Armanfard et al., 2016). The significance of this finding is not discussed here, but this study posed the question whether a similar phenomenon might be operative during general anesthesia and surgery. The pharmacokinetics of intermittent dosing, which is common, and the variable nature and timing of surgical stimulation might also create conditions where the MMN response is transient. Using the analytical techniques described in Chapter 3, no MMNs were observed during general anesthesia. This situation, however, brings attention to the most vexing issue in ERP research: inherent inter-trial variability and low signal to noise ratio necessitate averaging over time. Each analysis averaged data over the duration of one block, typically 35 minutes, which encompassed approximately 100 responses. Any one of those 100 responses could have been a classic MMN response, but in order to obtain any kind of statistical certainty, it would be subsumed in the epoch average. The underlying assumption that single-trial ERP responses are not representative of neural activity is challenged by Gaspar, who demonstrated high intra-subject reliability for ERP shapes in face recognition paradigms over time (Gaspar, Rousselet, and Pernet, 2011). Averaging, therefore, can result in loss of information which is transient and, in some circumstances, extremely

salient to the research question or application. New techniques in signal processing or machine-learning approaches continue to address this problem (Armanfard et al., 2016; Armanfard et al., 2019). Without some advancement in this area of ERP analysis, the MMN might not achieve full application potential in brain-computer interfaces and point-of-care testing.

5.4 Electrodes

In theory, an MMN response can be detected with one electrode. Though typically a fronto-central response, the spatial distribution of the MMN does vary (Duncan et al., 2009); so, if the goal of the study is to determine if such a response is present or absent, using multiple electrodes makes sense. Using multiple electrodes also allows channel interpolation if required. Using scalp sensors where an MMN response is not expected helps validate the experimental protocol and allows statistical contrasts. Finally, 64 electrodes is the minimum number of electrodes required to conduct source localization and connectivity studies, potential methodologies for future analyses.

5.5 Data Analysis

For the purpose of analysis, the primary study question - is a MMN response present? - is recast as a statistical question - can any deviant related neural activity be confidently distinguished from standard related activity? If deviant related activity is confidently identified, then typical latency and topographic criteria can be applied to determine if it qualifies as an MMN response. The approach taken focuses on single-patient averaged trials. Any mathematical treatment of the data must address two key challenges: the low signal to noise ratio and the multiple comparison problem. The MMN response is a low amplitude wave typically less than 8 microvolts and even less in disorders of consciousness. Noise sources include not only external sources but also internal sources of non-neural and neural origin. The latter consist of background brain activity and the inherent variability of the deviant response itself (Jackson and Bolger, 2014). In some ways, the only difference between "noise" and "signal" is the relevance of the measured data to the neural process of interest (Hebart and Baker, 2018). The high dimensionality of EEG data leads to the multiple comparison problem. A typical ERP experiment involves

comparing conditions, and those comparisons involve statistical tests comparing amplitudes at multiple sensors and time points. Correcting the p-value for 10^4 comparisons, a conservative number, would impose excessively strict criteria for statistical significance; while failure to correct risks false positives. These issues are significant and continue to challenge ERP researchers. Accordingly, ERP researchers focusing on single-trial analysis champion different approaches. These approaches broadly fall into two groups: improving the quality of the signal by de-noising; or improving the accuracy of various machine-learning classifiers. While not the focus of this study, these methods are nonetheless highly relevant.

Current consensus suggests that there is no best way to analyze ERP data. Gabriel's small but insightful study compared six different methods for identifying the MMN (Gabriel et al., 2016). The six methods were culled from recently published coma studies. One technique was visual and the other five were statistical. Gabriel reported on twenty-seven subjects, and in only 4 did all 6 methods detect an MMN; yet, in all subjects, at least two methods confirmed the presence of an MMN. While any one method showed varied ability to detect an MMN, the t-test on peaks performed the worst and the continuous wavelet transform performed the best. Gabriel notes that differences may be explained by different methods measuring different aspects of the neural response. Other studies support similar conclusions (Manresa et al., 2015). However, accuracy is not the only criterion relevant to selection of analytical techniques. Interpretability, computational speed, and scalability are equally important.

An approach that includes both visual inspection and multiple statistical techniques seems prudent. However, the traditional visual analysis of the ERP can be very misleading. This caveat applies to both epoch-averaged waveforms and difference waves. Without some quantification of the inter-trial variation at each time point, differences in amplitude between standard and deviant can appear significant when they are not, especially in the setting of low signal-to-noise measurements typical of MMN experiments. One study (Gramfort, Keriven, and Clerc, 2010) suggests that visual inspection of the "ERP image" (see Figure 4.1), which was part of the current protocol, provides a good compromise between visualizing individual epochs and trends in the time series. Though limited to the sensors of interest, this

visualization provided a "snap-shot" of the data and corresponded quite closely to the results of the statistical tests.

Each statistical treatment of the data offers a unique approach and addresses the criteria discussed above. Targeted t-tests are the easiest to calculate and interpret. These tests are tuned to the latency and spatial distribution of the MMN itself. Even without correction for multiple comparison, they are still useful in this setting where most t-tests were not significant. When simple t-tests are nonsignificant, more computationally elaborate error-controlling t-tests are unlikely to produce different results. Cluster permutation tests are probably the most statistically valid way to differentiate two conditions. Visualizations of clusters in time and space mesh with EEG data sets and are typically very informative. A bit more difficult to compute and interpret, they only allow the researcher to conclude that a difference exists and do not permit inferences on latency or peak amplitudes despite the detail that visualizations might show (Sassenhagen and Draschkow, 2019). Decoding, or multivariate pattern analysis, is a machine learning technique that aims to classify conditions by using sensor data as features. Interpretability and computational complexity vary according to the classifier, cross-validation, and prediction accuracy metrics. While classifying ERP responses based on spatial patterns appears conceptually straightforward, condition-dependent error, expressed in the variance and covariance of the datasets, can significantly affect classification accuracy (Hebart and Baker, 2018). Many parameters that fine-tune the classifier can have a huge impact on accuracy, and optimal parameters for ERP data are determined empirically. Multi-collinearity, which certainly exists amongst sensors due to volume conduction, limits the use of decoding to prediction as opposed to interpretation (Shmueli, 2010). Classic machine learning utilizing all discriminating features of the data, not just sensors, makes more sense but adds levels of complexity to the analysis. Nonetheless, decoding meets the desired criteria for this analysis and offers a definitive view of the data: control recordings were uniformly positive; test recordings were uniformly negative. In summary, types of analyses undertaken in this study were chosen for their individual strengths and were very different; but, remarkably, they produced the same results.

Chapter 6

Conclusions & Future Directions

Relying on high definition electroencephalography, a classic odd-ball paradigm, and contemporary methods of data analysis, this study could not demonstrate mismatch negativity during general anesthesia and surgery. The state of (un)consciousness produced by the required baseline anesthetic technique was likely sufficient to suppress this response. It was also likely sufficient to blunt a nociceptive response potent enough to activate neural components responsible for the MMN. These findings cast some doubt on the existence of sensory memory, and by inference other types of memory, during surgery and properly conducted general anesthesia.

As noted above (Chapter 5) the clinical setting of this study imposed limitations. Anesthetic drug levels and surgical stimulation could not be manipulated in any meaningful way. Employing a clinically validated measure the nociceptive state would have been beneficial. Measuring the degree of surgical stimulation and correlating peaks with the evoked EEG could have yielded information highly relevant to the study hypothesis. Of course, the time course of such peaks could be brief and transient; and so single trial analysis would need to be sufficiently refined to capture an correspondingly brief and transient evoked response. The rapid explosion in machine learning techniques and their adaptation to EEG data hold some promise in this regard.

Nonetheless, this study's findings are consistent with previous investigations. In sedation studies or studies of general anesthesia alone, the MMN tends to disappear with loss of responsiveness. And studies of other long-latency ERPs (e.g. N1 or P3a) during general anesthesia or general anesthesia and surgery

have also failed to identify persisting responses. No studies have attempted to measure MMNs during surgery and general anesthesia, perhaps because previous studies demonstrated that it disappeared prior to establishing drug levels associated with general anesthesia. Of note, the most recent ECoG studies show that the hierarchical processing characteristic of the MMN is absent during propofol anesthesia.

This study's findings are also consistent with the current body of research concerning the neurobiology of consciousness. Although controversies remain, the prevailing theory of anesthesia-induced unconsciousness posits that anesthetics disrupt corticocortical and corticothalamic networks. Normal functioning of these networks is required for the MMN response as it is currently understood.

Despite numerous challenges, acquiring good quality, high definition EEG is possible during routine surgery and anesthesia. This finding ensures continued studies of this nature in the future. Such studies might continue to investigate anesthesia-induced unconsciousness and focus on the dynamics of either the resting or evoked EEG using connectivity metrics, for example. General anesthesia continues to be a valuable model for investigating the neurobiology of consciousness, and the operating room is a natural place to conduct such studies.

Appendix A

Commonly Used Behavioral Scales of Alertness

MOAAS Level	**Response**
5	responds readily to name spoken in normal tone
4	lethargic response to name spoken in normal tone
3	responds only after name called loudly and/or repeatedly
2	responds only after mild prodding or shaking
1	responds only after painful stimuli
0	no response to painful stimuli

TABLE A.1: Modified Observer's Assessment of Alertness/Sedation Scale

Reference: Chernik, D.A., Gillings, D., Laine, H., Hendler, J., Silver, J.M., Davidson, A.B., Schwam, E.M., Siegel ,J.L. (1990). Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. J Clin Psychopharmacol, 10(4):244-51.

Ramsay Score	**Clinical Status**
1	patient anxious or/or agitated
2	patient co-operative, oriented, and tranquil
3	patient responds to commands only
4	a brisk response
5	a sluggish response
6	no response to light glabellar tap or loud auditory stimulus

TABLE A.2: Ramsay Sedation Scale

Reference: Ramsay, M., Savage, B., Simpson, B. ()1974). Controlled sedation with alphaxolene/alphdalone. Br. J Med., 42:656-659.

Appendix B

Summary of Referenced ERPs

Label	Time (ms)	Scalp Location	Neural Generator(s)	Functional Interpretation
P1, P50	50	FC	STC , MFC	sensory gating
N1 , N100	75 - 130	FC	STC	sensory reception
P2	150 - 275	C	STC	sensory reception
MMN	100 - 250	FC	STC , IFC	deviant detection
ERAN	100 - 200	FC	STC, IFC	music-syntactic processing
P3a, P300a	250 - 300	F	STC	attention
P3b , P300b	300 - 400	CP	STC, PFC THAL, HC	attention, memory
SW	500 - 600	CP		task-demand,memory

TABLE B.1: Basic Characteristics of Referenced ERPs

Abbreviations:
Label: *MMN* mismatch negativity, *ERAN* early right anterior negativity, *SW* slow wave; **Scalp Location:** *F* frontal, *C* central, *P* parietal; **Neural Generators:** *IFC* inferior frontal cortex, *MFC* medial frontal cortex, *PFC* prefrontal cortex, *STG* superior temporal cortex, *THAL* thalamus, *HC* hippocampus

Notes:
Many characteristics of an ERP, such as neural source and functional interpretation, depend on the task and condition by/under which the ERP is generated. Luck's discussion on this topic in his introductory text is particularly relevant. The text also provides a general, but similarly nuanced, discussion of a wide range of ERPs.

Label	**In-text References**
P1 , P50	VanHooff et al., 1997, Heinke et al., 2004
N1 , P100	Plourde and Picton, 1991, VanHooff et al., 1997, Simpson et al., 2002, Haenggi et al., 2004, Holečková et al., 2018
P2, P200	VanHooff et al., 1997
MMN	Simpson et al., 2002, Yppärilä et al., 2002, Heinke et al., 2004, Haenggi et al., 2004
ERAN	Heinke et al., 2004, Koelsch et al., 2006
P3a, P300a	Yppärilä et al., 2002, Koelsch et al., 2006, Holečková et al., 2018
P3b, P300b	Plourde and Picton, 1991, Holečková et al., 2018
SW	Plourde and Boylan, 1991

TABLE B.2: ERPs referenced in text

Abbreviations:
MMN mismatch negativity, *ERAN* early right anterior negativity, *SW* slow wave

Appendix C

ASA Physical Status Classification

ASA 1 healthy

ASA 2 mild to moderate systemic disease that does not limit activity

ASA 3 severe systemic disease that limits activity but is not incapacitating

ASA 4 systemic disease that is incapacitating and a constant threat to life

ASA 5 moribund; not expected to survive 24 hr. with or without surgery

Appendix D

Biosemi 64 Electrode Layout

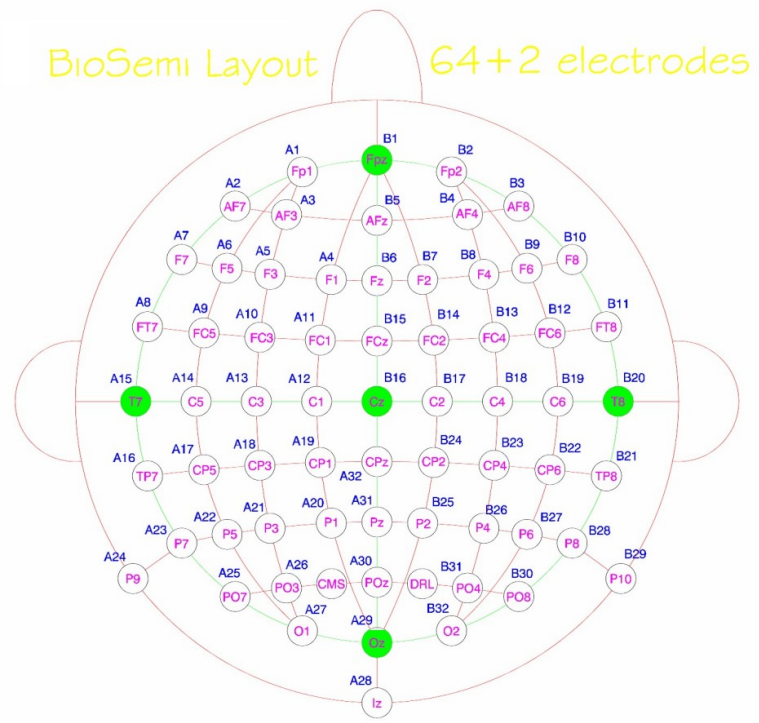


FIGURE D.1: Electrode Layout for BioSemi 64 Cap

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