PRESURGICAL DEPRESSION AND ANESTHETIC SENSITIVITY IN WOMEN UNDERGOING SURGERY FOR THE REMOVAL OF GYNECOLOGICAL TUMORS

By

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To my God, who reminds me daily that life is my stage,
and I am performing for an audience of One
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The present investigation examined the role of presurgical depression on anesthetic sensitivity. Based on theories of depression, frontal activity and anesthetic mechanisms, it was hypothesized that presurgical depression may place an individual at risk for greater responsiveness to initial anesthetic induction. Further, it was hypothesized that individuals with a history of depressive symptomatology would demonstrate greater sensitivity to initial anesthetic induction.

Twenty-six women between the age of 40 and 81 years ($M/SD = 58.9/10.9$) planning surgery under general anesthesia for the removal of gynecologic tumors completed measures of current depression one day before surgery. The measures used were the Beck Depression Inventory-Second Edition (BDI-II) and three scales of the Millon Behavioral Medicine Diagnostic (MBMD)—the Depression, Dejected, and Future Pessimism Scales. A preoperative health screening was used to classify women with ($N = 11$) or without ($N = 15$) a history of depression. Anesthetic sensitivity was quantified as an individual’s cumulative response to anesthetic drugs during the initial anesthetic induction phase and assessed with a unilateral frontal lobe EEG index derived from a bispectral index (BIS™) monitor. The dependent
variable, anesthetic sensitivity, was quantified using an ‘area over the curve’ (AOC) estimation based on individuals’ responses to anesthetic induction.

Higher reports of baseline presurgical depression were correlated with greater anesthetic sensitivity as measured by the MBMD Depression and Future Pessimism Scales ($r = 0.443$ and 0.474, respectively, $ps < 0.05$). However, there was no relationship found between the BDI-II or the MBMD Dejected Scale and anesthetic sensitivity. Further, there was no evidence of differences in anesthetic sensitivity among individuals with and without a history of depression.

These preliminary findings suggest that increasing levels of current presurgical depression may influence anesthetic sensitivity as defined by the AOC quantification. These findings indicate that premorbid factors may influence anesthetic management and, possibly, surgical outcome. Future studies need to examine the neurological mechanisms associated with premorbid anesthetic risk (e.g., frontal lobe EEG in depressed individuals having general anesthesia).
CHAPTER 1
INTRODUCTION

General anesthesia results in immobility, loss of consciousness, and reduced electrical activity in the brain (Grasshoff, Rudolph, & Antkowiak, 2005; McKechnie, 1992). In particular, anesthesia is known to suppress frontal lobe activity, a process that has been referred to as “depth of anesthesia” (Bruhn, Myles, Sneyd, & Struys, 2006), or anesthetic depth. One study suggests that greater anesthetic depth may be a clinically important predictor of increased incidence of 1-year mortality among non-cardiac surgical patients (Monk, Saini, Weldon, & Sigl, 2005). However, there is little research on the predictors of anesthetic depth. It has been hypothesized that patients who have less physiologic reserve (e.g., physically ill, older, cognitively impaired) may be more susceptible to the depressant effects of anesthesia (Muravchick, 1998), and may therefore experience greater anesthetic depth and possibly greater anesthesia-related morbidity and mortality. Premorbid patient factors that are associated with suppressed frontal lobe activity may heighten risk for greater anesthetic depth. Depression, for example, has previously been associated with reduced frontal activity (e.g., Davidson, 1998). Therefore, depression may compromise reserve and heighten risk for greater anesthetic depth among individuals undergoing surgery. The following review will examine the clinical assessment of anesthetic depth, explore the relationship between depression and frontal-specific brain function, and provide a rationale for examining response to anesthesia in women undergoing surgery for the removal of gynecologic tumors.

Clinical Assessment of Depth of General Anesthesia

Anesthetic depth has been conceptualized as the effect of anesthetic drugs on the brain cortex and is generally derived from a composite of patient responses to anesthetic drugs. Anesthesia acts on three parts of the nervous system, producing somewhat of a suppressor effect
as previously noted, vulnerable patient populations (i.e., those with advanced age or end-organ impairment, the terminally-ill, and those with otherwise compromised cognitive or physiologic reserve) tend to have an exaggerated drug effect from an “average” dose of anesthetic, and therefore require an adjustment in the dose of anesthetic to achieve a standardized depth of anesthesia (Muravchick, 1998). Indeed, research has shown that patients who are ill prior to surgery are more vulnerable to surgery itself (e.g., Newman et al., 1995). Bernstein and Offenbartl (1991), for example, examined the impact of patients’ presurgical comorbidities on postoperative outcomes. Comorbidities included severe mental and cognitive impairments, such as dementia. Although this was a retrospective investigation, a significant amount of fatal and nonfatal complications were associated with mental disorders, including dementia, schizophrenia, bipolar disorder and mental retardation. Of 59 of 975 general anesthesia cases
that resulted in some complication, 32 cases had presurgical dementia (25 of which resulted in mortality). Further, patients with presurgical cognitive impairments had an equal incidence of nonfatal complications as the surgery patients as a whole.

**Quantification of Depth of Anesthesia**

Within the last few years, several monitors have been developed to measure the effect of anesthetic drugs on cortical function (i.e., brain activity in the frontal cortex). Although it is neither designated as a routine patient monitor by the American Society of Anesthesiologists (ASA) nor considered a standard of care, the Bispectral Index Score (BIS™) monitor is clinically most widely used. The bispectral index score (BIS) is a dimensionless EEG-derived value, ranging from 0 (deep coma) to 100 (fully awakened), that measures the sedative component of the anesthetic state (i.e., hypnotic depth of anesthesia) via a unilateral electrode (Bruhn et al., 2006; Renna & Venturi, 2000). While informative, the BIS monitor has been shown to give misleading information. Though BIS values fall as a function of cortical suppression following anesthetic induction, a range of effects can be seen across individuals, drugs, and settings. For example, intraoperative BIS values may be exaggerated because of muscle activity (Messner, Beese, Romstock, Dinkel, & Tschaikowsky, 2003); baseline BIS values may be affected by neurological diseases (Renna & Venturi, 2000); and some anesthetics, most notably ketamine, do not cause dose-dependent BIS depression (Kelley, 2003). Furthermore, because BIS only measures the hypnotic component of an anesthetic, target ranges for intraoperative BIS values vary depending on the combination of drugs used. BIS values derived during a balanced anesthetic with a substantial opioid component typically range from 45 to 60, compared to fully awakened BIS values, which naturally range from 96 to 100. However, target values for BIS are less well defined for other anesthetic techniques (Kelley, 2003; Johansen, Sebel & Sigl, 2000;
Song, Joshi & White, 1997). Nonetheless, the interpretation of BIS values necessitates consideration of factors related to the patient, as well as the anesthetic used and has vast implications for anesthetic management.

**Clinical Significance of Depth of Anesthesia**

In 2005, Monk and colleagues reported findings that suggest an association between depth of anesthesia, measured as anesthetic drug effect on the brain cortex, and postoperative mortality within a year following surgery. These findings followed a prospective observational study of 1064 adult patients (18 years old or older) undergoing non-cardiac surgery under general anesthesia at Shands Hospital at the University of Florida. This study was designed to examine the relationship between postoperative mortality (defined as mortality within a year following surgery) and a variety of demographic, clinical, and intraoperative factors. The study employed use of the A1050 Bispectral Index Score (BIS™) monitor and sensors (Aspect Medical Systems Inc., MA) to quantify hypnotic depth of anesthesia. BIS data was recorded throughout the surgical intervention and digitized at 5-minute intervals. Anesthetic depth was calculated as cumulative deep hypnotic time, defined as the total amount of time (in hours) that BIS values fell below 45. A relative risk analysis was conducted using Cox proportional hazards modeling to determine the independent and combined impact of anesthetic depth, comorbid illness, demographic factors (e.g., age, race), clinical history (e.g., tobacco or alcohol use, preoperative blood pressure), and intraoperative factors (e.g., surgical duration, intraoperative blood pressure) on risk for postoperative death.

Results of this study indicated three variables as significant independent predictors of postoperative mortality—hypnotic depth of anesthesia (i.e., cumulative deep hypnotic time where BIS was <45), presence of comorbid disease, and intraoperative systolic hypotension. While the authors acknowledged that death during the first year after surgery was primarily associated with
pre-existing comorbidities and hypotension, not surprisingly, the finding relating anesthetic depth to increased mortality at one year garnered the most attention. The primary criticism of this study was that it was not designed to investigate the relationship between intraoperative anesthetic management and long-term outcome, suggesting incidental results at best. The use of a prospective observational method was particularly problematic in its failure to account for premorbid factors that might have contributed to the adverse outcomes observed. Thus, the conclusions were confounded by the use of the BIS™ monitor as convincing evidence for the observed relationship without a priori methodological control for known comorbidities, surgical diagnoses, anesthetic drugs, intraoperative anesthetic management, or other factors generally associated with mortality. Nonetheless, these associations suggest that intraoperative anesthetic management may affect long-term outcomes more than previously appreciated, which has vast implications for preventative intraoperative care.

A few other studies have at least attempted to address the relationship between anesthesia and adverse events. Rasmussen and colleagues (2003), for example, reported a greater incidence of postoperative cognitive dysfunction (POCD) at 1-week post-surgery, as well as postoperative mortality, after general anesthesia compared to regional anesthesia. However, no significant differences were observed between groups for other postoperative problems, including POCD at 3-months after surgery, delirium, and a number of medical complications (e.g., cardiac event). Despite these findings, Rasmussen and colleagues concluded that the etiology of POCD, as well as the incidence of mortality, were likely multifactorial rather than the result of anesthesia. In regard to the report of more deaths in the general anesthesia group, the investigators acknowledged that their study was not designed to evaluate uncommon postoperative complications (e.g., mortality). Further, the study provided no conclusive evidence that long-
term cognitive changes are caused by general anesthesia. Still, other studies indicated minimal risks associated with anesthesia during the perioperative period (Arbous et al., 2001; Sigurdsson & McAteer, 1996). Thus, the role of anesthesia on postoperative outcomes is, indeed, controversial. While some studies found minimal complications related to anesthesia (e.g., Rasmussen, 2003), others reported more significant outcomes related to anesthesia, to the greatest extent mortality (e.g., Monk et al., 2005).

Indeed, contrary to the results of the aforementioned studies, anesthesia-related mortality and complications may likely be explained by the interaction between anesthesia and premorbid factors, such as comorbid conditions and genetic or psychological factors, rather than by anesthesia alone. Simply stated, baseline impairment across a variety of domains may lead to negative outcomes. However, there continues to be a lack of attention to premorbid factors that may predict anesthetic depth, and consequently index risk for adverse outcomes such as mortality. Thus, consideration of the possible influence of premorbid patient factors on anesthetic responsiveness is warranted.

**Depression as a Possible Premorbid Marker of Risk**

Anxiety and depression are psychological factors known to affect the response to anesthetic drugs. For instance, patients with higher baseline preoperative anxiety have been shown to require more intraoperative anesthetic to achieve a clinically sufficient hypnotic state than patients with lower baseline preoperative anxiety (Maranets & Kain, 1999). In this cross-sectional study of 57 women undergoing bilateral laparoscopic tubal ligation, a differential response to anesthesia was demonstrated in groups low, moderate, and high on trait (i.e., characteristic) anxiety. These effects were seen for anesthetic induction, as well as maintenance, using the Aspect A1000 BIS™ monitor to control hypnotic depth of anesthesia. In regard to depression, a recent meta-analysis (Dickens, McGowan & Dale, 2003) reviewed the impact of
patient depression on experimental pain perception. Findings suggest that depressed patients may have a lower threshold for pain than non-depressed patients. This may have major implications for surgical interventions; namely, increased sensitivity to pain evidenced in depressed patients would necessitate delivery of enough intraoperative anesthetic to compensate for that effect. Hence, there is a need for research directed towards examining the relationship between presurgical depression and response to anesthesia (i.e., depth of anesthesia) and minimizing the impact of this risk factor.

**Depression and Frontal EEG**

Anesthesia specifically targets the frontal lobes (Drover & Ortega, 2006); and it has been hypothesized that depressed individuals may be particularly vulnerable to the effects of anesthesia. Depression has many known neurological components, which have been validated in a variety of literature examining the functional and structural role of the prefrontal cortices, anterior cingulate, amygdala, and hippocampus in affect and emotion regulation (Davidson, Pizzagalli, Nitschke, & Putnam, 2002). Of particular interest for the present study is the literature that has previously linked depression to abnormalities in electrical activation of the prefrontal regions of the brain (e.g., Davidson, Abercrombie, Nitschke, & Putnam, 1999; Davidson, 1998), which suggests that depression may be one possible risk factor for anesthesia-related complications. The predictive value of depression for response to anesthesia has not, however, been evaluated.

Previous research employing a variety of methods (e.g., cerebral blood flow and glucose metabolism) to elucidate the association between depression and cortical activity have yielded inconsistent findings. Still, there is substantial research indicating that depression is linked to neuroanatomical differences, particularly of the frontal region of the brain. The following
review will focus on research that has employed the use of multi-site electroencephalographs (EEG) to make inferences about patterns of regional cortical activation in the brain.

Notwithstanding controversy, much of this literature has related depression to neuroanatomical differences (i.e., abnormalities) in the prefrontal cortex of the brain. In particular, research suggests that the left hemisphere is involved in depression (e.g., Black, 1975; d’Elia & Perris, 1973, 1974; Gainotti, 1972; Gasparrini, Satz, Heilman, & Coolidge, 1978; Perini & Mendus, 1984; Robinson, Kubos, Starr, Rao, & Price, 1984). In a comprehensive review of this literature, Drevets (1998) noted that several studies provided evidence to support reduced frontal activation (with respect to alpha frequencies) of the prefrontal cortex in patients with major depressive disorder. To be clear, there is an inverse relationship between alpha power and region-specific activation (Davidson, 1988; Lindsey & Wicke, 1974). Some investigators, for instance, described abnormalities in activation of prefrontal regions in depressed individuals as decreased bilateral or predominantly left-sided activation (e.g., Davidson et al., 1999; George, Ketter, & Post, 1994). Indeed, the most consistent findings have related increased alpha power to left frontal hypoactivation, or less left-sided activity (e.g., Bell, Schwartz, Hardin, Baldwin, & Kline, 1998; Bruder et al., 1997; Davidson, Chapman, & Chapman, 1987; Davidson, Schaffer, & Saron, 1985; Gotlib et al., 1998; Schaffer, Davidson, & Saron, 1983). Fewer studies have demonstrated the opposite (i.e., increased alpha power associated with decreases in right frontal activation), a variation of previous findings, or an absence of abnormality or group differences altogether (e.g., Kentgen, Tenke, Pine, Fong, Klein, & Bruder, 2000; Reid, Duke, & Allen, 1998; Rochford, Swartzberg, Chowdhery, & Goldstein, 1976).

Davidson and colleagues, for example, have made significant contributions to this literature. To provide a few detailed examples, in the early 1990s, Henriques and Davidson
conducted several investigations to examine the differential activation of prefrontal cortical regions among depressed and healthy individuals. One of these studies examined whether asymmetrical activation of the prefrontal cortex discriminated between previously depressed and healthy controls (Henriques & Davidson, 1990). Following the notion that individuals with a history of depression (current or remitted) are at increased risk for future depression, the investigators also examined the utility of using region-specific electroencephalography (i.e., examination of cortical symmetry) as a state-independent marker of vulnerability to future depression. A small sample (N = 14) of participants (with and without a history of depression) was evaluated in respect to emotional state (before and during the EEG protocol), as well as brain activity (as measured by EEG using three reference points computed from 14 electrodes). Although power in all frequency bands was examined, results were only significant for alpha power, which is consistent with most literature in this area.

Findings showed participants with a history of depression demonstrated asymmetrical activation in the direction of more alpha power, or less left frontal and right posterior activation as compared to never-depressed control participants. Because the sample differed only in their history of depression (i.e., patients were carefully matched on several demographic variables, including age, gender, and socioeconomic status, and there were no significant differences in self-reported depression, emotional state, or medication history), these results suggest EEG is a reliable state-independent marker of depression history, which they proposed had implications for the prediction of future psychopathology or vulnerability to affective disorders. Later studies use the diathesis-stress model as a conceptual framework to explain how prefrontal asymmetry may bias affective style, and thereby increase vulnerability to psychopathology (e.g., Davidson, 1998).
In another study, Henriques and Davidson (1991) sought to demonstrate differences in left-sided frontal activation among depressed and never-depressed controls, with specific attention to the midfrontal and parietal regions. Following a similar procedure as the 1990 investigation, a small sample (N = 28) was evaluated. Patients with a history of depression (all of whom also met research criteria for current depression) demonstrated left frontal hypoactivation (i.e., more left-side alpha power, or less frontal activation) in the midfrontal region. Group differences were not detected in the parietal region. These findings support, at least partially, the investigators’ contention that cortical activation differs during approach- and withdrawal-related behavior, such that depressed individuals, who are more likely to demonstrate withdrawal-related behaviors (e.g., loss of initiative, difficulty concentrating, indecisiveness, hopelessness), will also demonstrate decreased left frontal activation.

While many studies have replicated findings demonstrating reduced left relative to right activation in depressed individuals (e.g., Bell et al., 1998; Bruder et al., 1997; Davidson, Schaffer, et al., 1985; Davidson, Chapman, et al., 1985; Debener, Beauducel, Nessler, Brock, Heilemann, & Kayser, 2000; Gotlib et al., 1998; Schaffer, Davidson, & Saron, 1983), it is worth noting that other findings are variable. For example, in addition to discussing the inconsistencies in the literature, Reid and colleagues (1998) failed to support their hypotheses that there would be region-specific group differences (here, mid-frontal and lateral-frontal regions) in regard to alpha activity (Study 1) or that this relationship would be apparent in a range of depressed individuals (Study 2). In the first study, they hypothesized that their depressed group would exhibit reduced left frontal activation relative to non-depressed controls. Results did not reveal group differences in those regions. They did, however, show differences in the parietal region. Further, among a sample of depressed individuals (Study 2), asymmetry was not related to
depression severity. These findings were surprising given the support for the hypotheses in the previous literature; however, there were few methodological differences (i.e., changes from previous methodologies) and limitations that may have contributed to these observations. One methodological difference, which appears to have had a significant influence on the findings, was the length of EEG recordings employed in the present study (8 min) compared to others (30 sec to 1 min). In fact, decomposition of intervals of EEG recordings into shorter blocks (2 min), revealed group differences commensurate to previous findings.

In sum, research conducted within the last 25 years has extensively illustrated the relationship between generalized slowing in the prefrontal cortex (i.e., asymmetrical activation of frontal regions of the brain) and depression. Despite the complexity of this literature and the variable findings, these studies have advanced our understanding of the neurological basis of depression. Indeed, use of electroencephalography to make inferences about patterns of regional cortical activation in the brain has significant implications for mediation of various outcomes (e.g., identification of individuals at risk for future depression). Though the relationship between cortical activity and depression has been largely substantiated in the literature, no attention has been directed towards implications for medical outcomes. For example, one can surmise that depressed individuals (who are predisposed to reduced frontal activation) may be particularly sensitive to anesthesia, which has a suppressing effect on the frontal cortex. Essentially, the underlying implication is that depression may be an index of anesthetic response, which has vast implications for healthcare delivery (i.e., anesthetic management). Furthermore, filling gaps in the literature is of particular importance in populations where depression is at least marginally prevalent.
Depression in the Gynecologic Oncology Population

Stress and depression are leading indicators of mortality, particularly among individuals diagnosed with cancer. Indeed, cancer patients experience numerous sources of acute and chronic stress (Spiegel, 1997; Vess, Moreland, Schwebel, & Kraut, 1988), which may manifest as a dysregulation of the circadian rhythmicity of cortisol secretion (Luecken, Dausch, Gulla, Hong, & Compas, 2004; Mormont & Levi, 1997; Ockenfels, Porter, Smyth, Kirschbaum, Hellhammer, & Stone, 1995; Sephton, Sapolsky, Kraemer, & Spiegel, 2000). Further, this dysregulation has been linked to both psychosocial stress and cancer progression, especially among patients with more advanced cancers (Sephton & Spiegel, 2003; Touitou et al., 1996).

Depression, the second psychological stressor indicated in mortality, has also been linked to dysregulated cortisol (Cohen, de Moor, Devine, Baum, & Amato, 2001), as well as to fatigue (Bower, Ganz, Dickerson, Petersen, Aziz, & Fahey, 2005), both of which are common features observed among individuals with cancer. It is not surprising then that depression, like stress, can negatively impact at-risk individuals by increasing risk for or complicating the course of cancer and its treatment and even speeding the progression of the disease (Katon & Sullivan, 1990). In addition, depression is linked to an increase in all-cause-mortality (Watson, Haviland, Greer, Davidson, & Bliss, 1999), which is particularly problematic among individuals with cancer.

Though the impact of depression on cancer prognosis is posited in the literature, little has been done in the way of addressing the impact of depression on individuals with imminent cancer diagnoses (i.e., those who are awaiting a conclusive diagnosis of cancer). In most cases, cancer diagnosis is preceded by a series of clinical tests to identify or assess the nature of clinical signs (e.g., presence of a tumor) and to determine the severity of pathology. This can be a potentially stressful process. As in the case of cancers etiologically related to an overgrowth of cells, surgical intervention to extract the tumor(s) is often necessary. Such cases warrant an
adequate evaluation of the relationship between stressful life events (conceptualized as the combination of physical, environmental, emotional, and psychosocial variables), physiologic/cognitive reserve, and prognosis, as well as factors that may impact medical outcomes (e.g., complications with anesthesia).

Though little is known of prevalence rates of depression among individuals awaiting cancer diagnosis (i.e., those with known clinical signs but awaiting conclusive diagnoses), prevalence rates for individuals with comorbid depression and a variety of cancer types have been estimated. For example, depression occurs in 12 to 23% of patients with gynecologic cancers (Massie, 2004). This means that a subgroup of the gynecologic oncology population (i.e., those who have gynecologic tumors) face the same prognostic risks as those already diagnosed with cancer. Additionally, because some proportion of these women will eventually receive a diagnosis of cancer, it is reasonable to expect the incidence of depression among them to be less than the upper limit of the range estimated for women with definitive cancer diagnoses (i.e., <23%). To be more specific, the prevalence of depression among women with gynecologic tumors could be estimated based on the known incidence of cancer diagnosis within this population. Based on an estimated 80% incidence of cancer diagnosis in this population, it is likely that 18.4% of these women have comorbid depression, which is enough to warrant clinical consideration.

Earlier, it was implied that depressed individuals might be particularly sensitive to anesthesia. This was based namely on the known predisposition of depressed individuals to reduced frontal activation, as well as the posited suppressing effect of anesthesia on the frontal cortex. While anesthesia-related complications have declined significantly over the last few decades (i.e., following the advent of more sophisticated intraoperative monitoring and
anesthetic management techniques), they are not uncommon, particularly among individuals who are more susceptible to the effects of anesthesia (e.g., depressed individuals). Though statistics do not indicate an enormous incidence of depression among gynecologic oncology patients (both with and without conclusive diagnoses), the incidence is large enough to merit attention. Particularly among patients awaiting a diagnosis, independent of direction (i.e. malignant or benign), this diagnostic period can be especially stressful (even more so for those who are already depressed), which may complicate the course of treatment. Thus, examination of depression as a premorbid risk factor for anesthesia-related complications can be useful in understanding differences in response to anesthesia, which ultimately has implications for prevention and intervention.

**Purpose of the Present Study**

The present study purposed to draw a conceptual link between depression, brain function (i.e., electrical activity in the frontal lobe), and depth of anesthesia. The former literature review sought to achieve the following objectives: (a) to define depth of anesthesia and explore how it has been quantified in previous research, (b) to examine and summarize the large body of literature linking depression to asymmetrical activation of the frontal cortex, and (c) to provide a rationale for examining response to anesthesia in women undergoing surgery for the removal of gynecologic tumors.

Despite the sufficient evidence available to propose a model linking the findings of the aforementioned areas, the impact of depression on a variety of intraoperative factors has been largely overlooked. In fact, the vast majority of research in areas of clinical interest, including postoperative cognitive dysfunction (POCD) and anesthetic awareness, has only addressed the psychological impact of these complications (e.g., post-traumatic stress disorder following anesthetic awareness), often glazing over or neglecting the preoperative piece (i.e., the impact of
comorbid disorders, as well as latent psychosocial factors such as a pre-existing history of depression). So, although previous research has shown an increased incidence of postoperative depression attributable to pain, complications of anesthesia, and other underlying causes across a variety of patient populations (Elkins, Whitfield, Marcus, Symmonds, Rodriguez, & Cook, 2005; Le Grand et al., 2006; Lindal, 1990; Miller, Jones, & Carney, 2005; Munro & Potter, 1996), no study to date has examined the relationship between presurgical depression and ‘anesthetic sensitivity’.

**Introduction to Anesthetic Sensitivity**

No line of research has formerly or directly documented a relationship between depression and ‘anesthetic sensitivity’. This can be attributed to the novelty of the concept. The present study proposed a model linking depression and anesthetic sensitivity via the conceptual framework of the literature linking depression to asymmetrical activation of the frontal cortex (Figure 1-1). Here, anesthetic sensitivity referred to an individual’s cumulative response to anesthetic drugs (measured in the same way as depth of anesthesia using digitized EEG derived from a patient state monitor) during the initial anesthetic induction phase (refer to methods outlined in Chapter 3 for a more detailed explanation). To be clear, the present study represented the first attempt to examine the demographic, biological, and psychological correlates of anesthetic sensitivity.

Specifically, the purpose of the present study was to examine the relationship between presurgical depression and anesthetic sensitivity in an at-risk population, some of which had a history of depressive symptomatology. To assess this, women over the age of 40 undergoing surgery for the removal of gynecologic tumors completed several self-report mood measures, with particular focus on depressive symptomatology, the day before their surgery. Additionally, intraoperative data related to the participants’ responsiveness to anesthesia was collected.
Participants were classified into two groups based on history of depressive symptomatology and compared on the basis of anesthetic sensitivity and current symptomatology. Identification of an interaction between depression and anesthetic depth is believed to improve our ability to predict anesthetic sensitivity, as well as to develop preoperative, as well as intraoperative, interventions to minimize associated outcomes.
Figure 1-1. Proposed model showing the major associations conceptualized in the present study.
CHAPTER 2
STATEMENT OF PROBLEM

The preceding review of literature provided a framework for undertaking the current investigation hypothesizing a relationship between depression and anesthetic sensitivity. As previously established, general anesthesia results in suppression of frontal lobe activity, a process that has been referred to as “depth of anesthesia” (Bruhn et al., 2006), which may be a clinically important predictor of increased incidence of intraoperative and postoperative complications. To the greatest extent, 1-year mortality among non-cardiac surgical patients has been reported to be related to increased anesthetic depth (Monk et al., 2005). Though much is known about the mechanisms of anesthesia, there is little research on the predictors of response to anesthesia. To this end, it has been hypothesized that patients who have less physiologic or cognitive reserve may be more susceptible to the depressant effects of anesthesia (Muravchick, 1998). As previously alluded, premorbid patient factors that are associated with suppressed frontal lobe activity, such as depression, may heighten risk for greater anesthetic depth (identified here as ‘anesthetic sensitivity’). Hence, the present study examined the impact of depression on anesthetic sensitivity in a sample of women undergoing surgery for the removal of gynecologic tumors.

No line of research has formerly or directly documented a relationship between depression and anesthetic sensitivity. It is, indeed, a novel concept. Here, anesthetic sensitivity was defined as an individual’s cumulative response to anesthetic drugs during the initial anesthetic induction phase. It was measured in much the same way as depth of anesthesia (using digitized EEG derived from a patient state monitor) and was calculated with respect to ‘area over the curve’ (AOC) of BIS during the anesthetic induction phase (more on this in the following chapter). Further, this study assessed the effect of history of depression on anesthetic sensitivity by
classifying participants into two depressed groups (depressed versus not depressed) based on an interview. The incidence of depression among surgical patients (particularly those who have or are at risk for cancer) is also thought to be significant, and thus the effects of anesthesia on this sample was reasonably expected to be apparent. Although correlational analyses do not provide causal evidence for the relationship between depression and anesthetic sensitivity, the current study might represent a significant movement towards identifying areas for clinical intervention at the preoperative, intraoperative, and postoperative levels.

The current study addressed the following specific aims:

**Specific Aim I**

To examine the relationship between presurgical depression and anesthetic sensitivity in an at-risk population (i.e., gyn-oncology). Given the known effect of anesthesia on the frontal lobe (e.g., McKechnie, 1992) and the association between depression and reduced frontal activity (e.g. Davidson, 1998), it was hypothesized that depression severity would be positively related to greater sensitivity to anesthesia. Specifically, it was predicted that individuals who report more depressive symptoms prior to surgery would show greater responsiveness to initial anesthetic induction, measured as ‘area over the curve’ (AOC).

**Specific Aim II**

To evaluate whether anesthetic effects differ among individuals with and without a history of depressive symptomatology. It was hypothesized that there would be group differences in response to anesthesia. Specifically, it was predicted that individuals with a history of depressive symptomatology would demonstrate greater sensitivity to initial anesthetic induction, also measured as AOC.
CHAPTER 3
METHODS

Sample Characteristics

Participants were a subgroup of 76 women concurrently enrolled in an ongoing longitudinal study of anesthetic management, cognitive dysfunction, and mortality. They included 26 women, all above the age of 40, undergoing lower abdominal surgery for the removal of gynecologic tumors (i.e., one or a combination of the following procedures (not exhaustive): total or partial abdominal hysterectomy, bilateral salpingectomy/oophorectomy, exploratory laparoscopy, appendectomy, lymph node dissection/sampling, cytoreduction, appendectomy, omentectomy, and colectomy). Eleven of these women were identified as having a history of depressive symptomatology based on a consensus conference that took into account a report of a combination of factors, including current and/or past depressive symptomatology, diagnosis of clinical depression, and self-reported treatment for depressive symptomatology, including a history of antidepressent use as determined by self-report and/or review of available medical records. The remaining age- and education-matched participants were 15 women with no known history of depressive symptomatology.

The following inclusion and exclusion criteria were applied. Participants were required to be over the age of 40 and native English speakers. Also, participants were also required to score $\geq 24$ on the Mini-Mental State Exam (MMSE). Additional exclusion criteria applied exclusively to fulfill research aims for the larger longitudinal study included (a) severe cardiovascular compromise or an ejection fraction of $< 20\%$, (b) need for regional anesthesia and/or emergency surgery, (c) malignant hyperthermia, (d) choline esterase deficiency, (e) porphyria, (f) allergy to lidocaine, (g) inability to tolerate a normal dose of hypnotic during anesthetic induction (based on the clinical judgment of the attending anesthesiologist), and (h) conditions that would
confound interpretation of neurocognitive tests such as blindness, severe hearing impairment, and brain metastases.

Forty-three of the 76 women enrolled in the larger longitudinal study consented to participate in additional psychological and neurocognitive testing. Although all were eligible, 17 possible participants were excluded from the current analysis. The remaining 26 participants were between the age of 40 and 81 years ($M/SD = 58.9/10.9$), of average intelligence ($M/SD = 103.3/19.0$), and, on average, were at least high school educated ($M/SD = 12.7/2.3$ years). The sample represented a variety of ethnic backgrounds, including 19 Caucasian participants, 4 African-American participants, one Hispanic participant, one Native-American participant, and one participant of Pacific Island origin. There were no significant differences between the groups with and without a history of depressive symptomatology with respect to age [$t(24) = 1.43$, $p = 0.17$], intelligence (as measured by the Wechsler Abbreviated Scale of Intelligence; WASI) [$t(17) = 1.67$, $p = 0.11$], and presence of comorbid disease (as measured by the Charlson Comorbidity Index; CCI) [$t(24) = 1.06$, $p = 0.30$]. The group with a positive history of depressive symptomatology was, however, relatively less educated [$t(19) = 2.66$, $p = 0.02$]. Table 3-1 summarizes participant characteristics.

**Procedures and Assessment Instruments**

Participants were systematically recruited via close collaboration with the scheduling staff of the UF-Shands Gynecologic Oncology Clinic and the principal investigators of the larger longitudinal study examining ‘Anesthetic Depth and Mortality’ in this patient population. As part of this larger investigation, all patients were to have gynecological surgery to identify, to

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1 Thirteen participants were excluded because their Bispectral Index Scores (BIS) records were invalid, inaccessible, or missing. Three participants did not complete psychological measures. One participant did not meet the minimum criteria for MMSE score $\geq 24$. 

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remove, and identify the pathology of gynecological masses. During a routine examination and assessment for surgery, patients meeting study criteria were identified and invited to participate in the study. Interested participants provided informed consent for participation following University of Florida Institutional Review Board guidelines. Consented participants were scheduled for admission to the General Clinical Research Center (GCRC), where they completed a brief clinical interview and neurocognitive and psychological testing the day before their surgery. Before the surgical procedure, all participants received the same weight-based induction of anesthesia. Anesthesia was then maintained with one of three randomized, prescribed anesthetics. The same surgeon performed all procedures. See Figure 3-1 for an overview of the study design.

**Clinical Interview and Consensus Conference**

Participants underwent a presurgical clinical interview to obtain relevant background and demographic information, medical and psychiatric history, as well as family health history. A thorough review of history of depression, anxiety, and other mood disorders was made. Participants endorsing a history of depression as defined by self-report of current and/or past depressive symptomatology (but not exclusively current symptomatology), diagnosis of clinical depression, and/or treatment for depressive symptomatology, including a history of antidepressent use or psychotherapy focused on addressing clinical depression were considered for classification in the history of depressive symptomatology group. In some cases, classification was made on the basis of findings from a review of available medical records. Final determination of group classification was made via consensus conference. Post hoc comparisons of groups were made on the basis of these classifications.
Psychological Assessment Measures

Several mood measures were administered to participants the day before surgery to assess baseline mood status, including the Beck Depression Inventory—Second Edition (BDI-II) and the Millon Behavioral Medicine Diagnostic (MBMD).

**Beck Depression Inventory—Second Edition (BDI-II; Beck, Steer, & Brown, 1997):**
The BDI-II is a 21-item self-report inventory. It is the most widely used screening instrument to detect depressive symptomatology and is commonly used to assess cognitive and somatic dimensions of depression occurring within two weeks of administration. The BDI-II has been reported to have exceptional reliability and validity (Beck et al., 1997).

**Millon Behavioral Medicine Diagnostic (MBMD; Millon, Antoni, Millon, Meagher, & Grossman, 2001):** The MBMD is a 165-item, self-report, true/false questionnaire used to assess the psychological factors that may influence the course of treatment of medically ill patients. It contains 38 scales that tap into the following dimensions: response patterns, negative health habits, psychiatric indications, coping styles, and stress moderators. The MBMD has been used extensively in health psychology research, as well as clinically to help identify factors that may impact health care delivery. The MBMD has demonstrated adequate reliability and validity (Millon et al., 2001). The subscales of interest for this study were the Depression Scale, the Dejected Scale, and the Future Pessimism Scale, the predominant psychiatric indicator, coping style, and stress moderator, respectively, in this patient population. Though these scales are highly correlated, they have been shown to tap into unique dimensions of behavior and will, therefore, be assessed independently.

The Depression Scale is one of five psychiatric indicators of the MBMD. This scale focuses on the patient’s cognitive and somatic state, as indicated by changes in appetite, feelings of hopelessness, social isolation, anhedonia, self-deprecation, and a number of other depressive
symptoms. Examples of MBMD Depression Scale items include, “I’ve lost interest in things that I used to find pleasurable” and “I have been having serious thoughts about suicide.” Though elevation on this scale does not warrant a conclusive diagnosis of clinical depression, as defined by the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition Text Revision (DSM-IV-TR; American Psychiatric Association, 2000), the scale provides supportive evidence for a diagnosis of depression.

The Dejected Scale, one of the 11 coping styles subscales, is designed to identify patients that are predisposed to pessimism and demonstrate marked inability to persevere in the face of personal problems (e.g., medical diagnosis) as indicated by persistent and sometimes characteristic disheartenment, hopelessness, and disconsolation. Sample items on this scale include “I spend much of my time brooding about things” and “My life has always gone from bad to worse.”

Finally, the Future Pessimism Scale assesses patients’ present outlook toward their prognosis and future health status. Research has shown this stress moderator to influence several medical outcomes, including adherence to and confidence in medical recommendations, emotional response to medical diagnosis, as well as disease course. Unlike the Depression and Dejected Scales, the Future Pessimism Scale is a relatively less global assessment of patient’s response style, reflecting rather patient’s current response to a current medical diagnosis. Sample items on this scale include “Life will never be the same again for me” and “My future looks like it will be full of problems and pain.”

Taken together, these subscales of the MBMD have vast implications for assessment of patients’ prognosis in the context of health maintenance (e.g., adherence to medical regimen) and healthcare delivery (e.g., improving communication between patients and healthcare providers).
Other Questionnaires

Charlson Comorbidity Index (CCI; Charlson, Pompei, Ales, & MacKenzie, 1987): The CCI is a 17-item questionnaire designed to identify and classify comorbid conditions that may alter the risk of mortality, or disease process. Comorbidity is defined as the presence of one or more disorders, or diseases, in addition to a primary medical diagnosis. The measure indexes diseases such as coronary artery disease (CAD), peripheral artery disease, cerebrovascular disease, pulmonary disease, diabetes, and metastatic solid tumor, among others, which are assigned a score based on severity (e.g., mild liver disease = 1; HIV/AIDS = 6).

Neuropsychological Assessment Instruments

In addition to psychological assessment measures, participants were administered several neuropsychological tests to assess baseline cognitive status, including a brief assessment of baseline mental status, using the Mini-Mental State Exam (MMSE), as well as intellectual ability, using the Wechsler Abbreviated Scale of Intelligence (WASI). For the current study, only the MMSE and the WASI will be discussed as they provide an index of global cognitive function from which to match comparison groups.

Mini-Mental State Exam (MMSE; Folstein, Folstein & McHugh, 1975): The MMSE provides a structured approach to mental status testing and screening for general cognitive decline. It is comprised of 11 simple questions, yielding a maximum score of 30. The MMSE was used to characterize general, global changes in cognitive function relative to temporal orientation, verbal memory, attention, language, and visuoconstruction ability. Individuals with MMSE score < 24 were excluded from the study.

Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999): The WASI is a short (approximately 30 minutes) and reliable measure of general intelligence. It has four subtests: Vocabulary, Block Design, Similarities, and Matrix
Reasoning. Like other widely used Wechsler scales, the WASI is nationally standardized and provides summary scores for Verbal IQ, Performance IQ, Two-subscale IQ and Full Scale IQ. A Two-subscale IQ based on performance on the Vocabulary and Matrix Reasoning subtests was used in the current study.

**Outcome Variable—Anesthetic Sensitivity**

The current investigation involved the measurement of anesthetic sensitivity, defined as an individual’s initial responsiveness to anesthesia from presurgical baseline to the intraoperative anesthetic maintenance phase. Anesthetic sensitivity was measured intraoperatively using a Bispectral Index Score (BIS™) monitor (Aspect Medical Systems Inc., MA), a digitally processed electroencephalograph (EEG) parameter used to quantitatively measure hypnotic depth of anesthesia (i.e., the direct effects of anesthetics on the brain cortex) during surgical procedures. BIS is represented as a value between 0 and 100 and is calculated as a rolling average of raw (i.e., artifact-free) EEG data, or the smoothing rate. BIS values generally fall in the range of 96 to 100 for fully awakened individuals and falls variably as frontal wave activity declines (i.e., in response to anesthetic induction). Standardized placement of the unilateral BIS™ sensor for this protocol was across the participant’s left frontal lobe. Baseline BIS was recorded immediately after the BIS™ sensor was mounted onto patients (i.e., before surgery) and subsequent BIS were digitally recorded through the duration of the surgical intervention using the 30-second smoothing rate (as opposed to the 15-second smoothing rate), which decreases variability.

Data was abstracted from the BIS™ monitor and downloaded to a database for use in the current analysis. For the purpose of the primary aim of this investigation, BIS was quantified as ‘area over the curve’ (AOC), or the difference between the total area and ‘area under the curve’
(AUC) as conceptualized by Pruessner, Kirschbaum, Meinlschmid, and Hellhammer (2003), who proposed two formulas for calculation of AUC. The current study employed the formula for ‘AUC with respect to ground’ (AUC\textsubscript{G}), in which individuals’ responsiveness to anesthesia is examined during the critical period defined as baseline to anesthetic maintenance, designated as 6.5 minutes post-anesthetic induction. Because variability in intraoperative factors increases greatly during anesthetic maintenance, this cutoff was determined to be an acceptable threshold to observe the effects of initial anesthetic induction as illustrated in Figure 3-2.

**Statistical Analyses**

The psychological assessment measures used to assess mood in the current study (i.e., the BDI-II and the MBMD) were hand-scored following scoring instructions provided in the respective administration and scoring manuals. Raw scores for both measures were entered as continuous variables in order to examine Aim I, with higher scores indicating increasing symptom severity. The formula for calculation of ‘area under the curve in respect to ground (AUC\textsubscript{G})’ was used to estimate ‘area over the curve (AOC)’ (see Figure 3-3).

The statistical software package SPSS 14.0 for Windows (SPSS Inc., IL) was used to conduct the statistical analysis for this research study.

**Specific Aim**

To examine the relationship between presurgical depression and anesthetic sensitivity in an at-risk population (i.e., gyn-oncology) regardless of group assignment, Pearson’s correlations were used. Given the known neurological component of depression and the expansive research on the impact of compromised cognitive/physiologic reserve on anesthetic responsiveness in vulnerable populations, it was hypothesized that depression severity would be positively related to greater sensitivity to anesthesia, as determined by AOC estimates.
Specific Aim II

To evaluate magnitude of anesthetic effects (i.e., responsiveness to initial anesthetic induction) among individuals with and without a history of depressive symptomatology, group comparisons were made using an independent samples t-test.
Table 3-1. Participant characteristics by group—Means and standard deviations shown.

<table>
<thead>
<tr>
<th></th>
<th>No History of Depressive Symptomatology (N=15)</th>
<th>History of Depressive Symptomatology (N=11)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.4 (9.9)</td>
<td>55.4 (11.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Years of Education</td>
<td>13.6 (1.9)</td>
<td>11.3 (2.2)</td>
<td>p = 0.016</td>
</tr>
<tr>
<td>IQ</td>
<td>109.2 (16.9)</td>
<td>95.1 (19.7)</td>
<td>ns</td>
</tr>
<tr>
<td>CCI Total</td>
<td>5.1 (2.3)</td>
<td>4.0 (2.8)</td>
<td>ns</td>
</tr>
</tbody>
</table>

IQ, Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999)
CCI, Charlson Comorbidity Index (Charlson et al., 1987)

Figure 3-1. Study design flowchart.²

² Seventeen possible participants were excluded from the current analysis. Thirteen participants were excluded because their bispectral index score (BIS) records were invalid, inaccessible, or missing. Three participants did not complete psychological measures. One participant did not meet the minimum criteria for MMSE score ≥24.
Figure 3-2. Illustration of ‘area under the curve with respect to ground’ ($AUC_G$) and ‘area over the curve’ (AOC).

$$AUC_G = \sum_{i=1}^{n-1} \frac{(m_{i+1} + m_i) t_i}{2}$$

$AOC = total\ area - AUC_G$

Pruessner et al., 2003.

Figure 3-3. Formulas for ‘area under the curve with respect to ground’ ($AUC_G$) and ‘area over the curve’ (AOC)
CHAPTER 4
RESULTS

Independent samples t-tests confirmed group differences in mood in some, but not all of the administered questionnaires. Table 4-1 shows the results of these independent samples t-tests. Consistent with expectations, there were significant differences between the groups for depression as measured by the Beck Depression Inventory—Second Edition (BDI-II), \[ t (24) = -2.89, p < 0.05; r = .51 \], as well as the Millon Behavioral Medicine Diagnostic (MBMD) Depression and Dejected Scales, \[ t (24) = -2.90, p < 0.01; r = 0.51 \] and \[ t (24) = -2.69, p < 0.05; r = 0.48 \], respectively. These represent moderate effects. There were no significant differences between groups, however, for the Future Pessimism Scale \[ t (24) = -0.895, p = 0.380; r = 0.18 \]. Differences between groups for the somatic and cognitive indices of the BDI-II were also detected \((ps < 0.05)\) and are reported in Table 4-1. It is noteworthy that for all significant differences, the group with a history of depressive symptomatology demonstrated a trend towards significantly more depression at the mean level across measures. It should also be noted that mean reports of depression on both the BDI-II and the MBMD did not reach clinical significance for either group.

**Specific Aim I: Relationship Between Depression and Anesthetic Sensitivity Independent of Group Classification**

Pearson’s correlational analyses were conducted to assess the relationship between depression and anesthetic sensitivity. Anesthetic sensitivity was measured with respect to calculations of ‘area over the curve’ (AOC), which was mathematically derived from the ‘area under the curve with respect to ground’ (AUCc) formula for each participant (Pruessner et al., 2003; also, see Chapter 3, Methods, page 36). All variables of interest were relatively normally distributed. It was hypothesized that depression severity would be positively related to greater sensitivity to anesthesia, as determined by AOC estimates. Depression severity was
operationalized using scores on the BDI-II, as well as three scales of the MBMD (i.e., Depression, Dejected, and Future Pessimism). Results indicated an association between two of the MDMD scales, the Depression and Future Pessimism Scales ($p < 0.05$). Specifically, higher reports of baseline presurgical depression (as measured by the MBMD Depression Scale; $r = 0.443, p = 0.02$) and greater pessimism towards current medical diagnosis ($r = 0.474, p = 0.02$) were correlated with greater anesthetic sensitivity. See Figures 4-1 and 4-2 for visual illustrations of these trends. There were no significant relationships found between depression severity as measured by the BDI-II ($r = 0.122, p = 0.551$) or the Dejected Scale of the MDMD ($r = 0.141, p = 0.492$) and anesthetic sensitivity.

**Specific Aim II: Relationship Between Group Classification and Anesthetic Sensitivity**

The relationship between group classification and anesthetic sensitivity was assessed using an independent samples t-test with group classification as the independent variable and AOC estimate for anesthetic sensitivity as the dependent variable. Greater AOC estimates were predicted for the group with history of depressive symptomatology; stated differently, greater responsiveness to the initial effects of anesthetic induction would be seen in the group with history of depressive symptomatology. The independent samples t-test failed to reject the null hypothesis. Explicitly, there was no significant group difference in AOC estimates. AOC estimates were no different for participants without a history of depressive symptomatology ($M = 527.26, SD = 105.42$) as compared to those with a history of depressive symptomatology ($M = 569.47, SD = 127.73$), [$t (24) = -0.923, p = 0.37$] (see Figure 4-3).

A correlational analysis was conducted to examine possible factors that might contribute to the effect of depression on anesthetic response. Age, comorbid illness (as measured by the Charelson Comorbidity Index, CCI), and pathology status (i.e., whether tumor was benign or malignant) were examined. None of these possible covariates were related to the outcome...
variable of AOC (all $p < 0.05$; see Table 4-2). These results, therefore, preclude examination of the impact of patient factors such as age, the presence of comorbid illness, and pathology status on group differences in AOC at this time. Possible reasons for the lack of group differences in anesthetic sensitivity are addressed in the next chapter.

Table 4-1. Means and standard deviations for psychological assessment measures.

<table>
<thead>
<tr>
<th>Psychological Assessment Measures</th>
<th>No History of Depressive Symptomatology ($N=15$)</th>
<th>History of Depressive Symptomatology ($N=11$)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI-II (Total)</td>
<td>7.0 (5.5)</td>
<td>19.7 (13.8)</td>
<td>$p = .013$</td>
</tr>
<tr>
<td>BDI-II (Somatic)</td>
<td>4.9 (3.1)</td>
<td>8.5 (4.7)</td>
<td>$p = .025$</td>
</tr>
<tr>
<td>BDI-II (Cognitive)</td>
<td>2.1 (2.9)</td>
<td>11.2 (9.6)</td>
<td>$p = .011$</td>
</tr>
<tr>
<td>MBMD Depression</td>
<td>30.8 (23.7)</td>
<td>59.9 (27.3)</td>
<td>$p = .008$</td>
</tr>
<tr>
<td>MBMD Dejected</td>
<td>10.5 (18.9)</td>
<td>43.6 (37.6)</td>
<td>$p = .018$</td>
</tr>
<tr>
<td>MBMD Future Pessimism</td>
<td>48.3 (25.4)</td>
<td>56.9 (22.8)</td>
<td>$ns$</td>
</tr>
</tbody>
</table>

Table 4-2. Correlation matrix for AOC and hypothesized covariates.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>CCI Total</th>
<th>Pathology Status</th>
<th>AOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00</td>
<td></td>
<td></td>
<td>0.052</td>
</tr>
<tr>
<td>CCI Total</td>
<td>0.288</td>
<td>1.00</td>
<td>0.730**</td>
<td>-0.361</td>
</tr>
<tr>
<td>Pathology Status</td>
<td>0.383</td>
<td>0.730**</td>
<td>1.00</td>
<td>-0.023</td>
</tr>
<tr>
<td>AOC</td>
<td>0.052</td>
<td>-0.361</td>
<td>-0.023</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Correlation is significant at the 0.01 level (2-tailed).**

CCI, Charlson Comorbidity Index (Charlson et al., 1987)
Figure 4-1. Relationship between MBMD depression scores and anesthetic sensitivity (AOC).
Figure 4-2. Relationship between MBMD future pessimism scores and anesthetic sensitivity (AOC).

$$r = 0.474, p = 0.02$$
Figure 4-3. Relationship between group classification and anesthetic sensitivity (AOC).

Note: Error bars represent standard error of the mean.
CHAPTER 5
DISCUSSION

The present study examined two aims. The first aim examined the relationship between presurgical depression severity and anesthetic sensitivity in a group of women undergoing surgery for the removal of gynecologic tumors. Given the known effect of anesthesia on the frontal lobe (e.g., Grasshoff et al., 2005; McKechnie, 1992) and the association between depression and altered frontal lobe activity (e.g. Davidson, 1998), it was hypothesized that individuals with presurgical depression would be more sensitive to anesthesia. That is, these individuals would demonstrate a greater decline in their frontal lobe EEG frequency, as measured by a Bispectral Index monitor (BIS; Aspect Medial Systems Inc., MA) immediately following anesthetic induction. For the present investigation, an ‘area over the curve’ (AOC) algorithm was used to quantify EEG change from a pre-anesthesia baseline to 6.5 minutes post-anesthetic induction.

The second aim examined whether anesthetic effects would differ among individuals with and without a history of depressive symptomatology. It was hypothesized that there would be group differences in response to anesthesia such that individuals with a history of depressive symptomatology would demonstrate greater sensitivity to initial anesthetic induction.

Summary and Interpretation of the Results

Specific Aim I

The hypothesized positive relationship between presurgical severity of depression and anesthetic sensitivity was supported by two of the four depression scales. Depression severity was operationalized using scores on three scales of the MBMD (Millon et al., 2001)—the Depression, Dejected, and Future Pessimism Scales—as well as the BDI-II (Beck et al., 1997). Results provided some support for an association between depression and anesthetic sensitivity.
Specifically, participants’ self-reports on the Depression and Future Pessimism Scales of the MBMD were related to anesthetic sensitivity. This pattern was not observed, however, when assessed with the BDI-II and the Dejected Scale of the MBMD. Thus, although all four measures were highly correlated, only data from the Depression and Future Pessimism Scales (MBMD) supported the proposed hypothesis.

There is some indication that findings may be at least partially attributable to scale differences. Compared to the BDI-II, the MBMD Depression Scale is a subtler, less face valid measure of patient mood status. It provides a more global picture of a patient’s mood (Millon et al., 2001); and, unlike the BDI-II, it represents a personality style, in addition to tapping into acute symptoms of depression. Compared to even the other indices of depression on the MBMD, the Depression Scale focuses on the patient’s mood state (e.g., decreased appetite, discouragement, anhedonia), with particular sensitivity to characteristic signs of depression. Examples of MBMD Depression Scale items include, “I’ve lost interest in things that I used to find pleasurable” and “I have been having serious thoughts about suicide.” Similarly, the Future Pessimism Scale of the MBMD also provides an assessment of patient’s outlook towards current medical diagnosis. In fact, previous research has shown this stress moderator to influence several medical outcomes, including disease course (Millon et al., 2001). Sample items on this scale include “Life will never be the same again for me” and “My future looks like it will be full of problems and pain.”

These findings are very promising. Though results were measure-specific, the observed association between higher scores on the MBMD Depression and Future Pessimism Scales and increased anesthetic sensitivity suggests that these measures may discriminate those who are at greatest risk for anesthesia-related complications. Why depression may relate to anesthetic
sensitivity could be explained by anatomical differences (i.e., of the frontal cortex) in those who report greater severity of depressive symptomatology. Indeed, those who report greater depression may likely evidence increased vulnerability to anesthesia, which acts on the frontal lobe. This may have important implications for future research in the area of anesthetic sensitivity, which will be addressed in the following section.

**Specific Aim II**

Results of the secondary analysis did not provide evidence to support the second hypothesis of the current study. Individuals who were classified as “depressed” based on interview information did not demonstrate a greater responsiveness to anesthesia when compared to “non-depressed” individuals. This may be partially explained by intragroup variability in AOC estimates, as well as sample size limitations. As Figure 4-3 illustrates, there was much overlap between the groups in terms of AOC, with the group with a positive history of depression showing much more variability in AOC.

The fact that there is a relationship between some indices of depression and anesthetic sensitivity would suggest that individuals with a history of depressive symptoms would demonstrate greater sensitivity to anesthesia. Indeed, a number of factors could contribute to the aforementioned relationship (i.e., between depression severity and anesthetic sensitivity). The cerebral reserve literature (e.g., Stern, 2002; Satz, 1993), for instance, would suggest that factors such as age, education, intelligence (IQ), and comorbidity could account for group differences in the outcome. An exploratory analysis evaluating the relationship of the outcome variable, anesthetic sensitivity, with the aforementioned covariates did not reveal any significant relationships. Although education was found to be significantly different between groups with or without a history of depression (with the group having a history of depression being less educated), the lack of a relationship between education and the outcome variable suggests that it
is not a significant contributor to the observed relationship between depression severity and anesthetic sensitivity. This strengthens the finding by allowing us to attribute anesthetic sensitivity to depression, and possibly reduced frontal activity in the brain.

Still, the lack of group differences in anesthetic sensitivity warrants attention. Specifically, the variability in AOC estimates in the group with a history of depressive symptoms needs to be addressed. One possible explanation is the composition and size of the group with a history of depression. Few of the participants classified in this group actually reported clinically significant depression (i.e., scale scores >75) when the MBMD was administered\(^3\). The criteria applied in the consensus conference to classify participants into the groups with and without a history of depression were very sensitive. Considerations included current symptomatology, previous history of depressive symptoms, and formal diagnosis and/or treatment (i.e., therapy and/or medication) for clinical depression. Despite the attention to multiple factors in making group assignments, reports of current symptomatology within the group with a history of depression were variable. This suggests that differences in response to anesthesia may be manifested differentially among those that have a history of sub-clinical depression versus those with a history of severe depression. That is, there may be within-group differences in anesthetic sensitivity.

Though participants in each group endorsed levels of current depressive symptomatology on the depression measures commensurate with their classification, the consensus conference method was imperfect. Classification of participants may have been confounded, in some cases, by limited evidence for classifying participants in one or the other group. For example, for a

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\(^3\) Of the 11 participants in the group with a history of depression, 3 participants reported clinically significant levels of depression as measured by the MBMD Depression Scale; and 1 participant reported clinically significant levels of depression as measured by the Future Pessimism Scale.
subgroup of participants who did not complete a full clinical interview (i.e., with detailed query of psychological history), the consensus was based on available medical records, which generally favored a classification into the group with no history of depression. The possibility of misclassification, in addition to variability in depression and sample size limitations, may have played a significant role in the current findings.

**Implications and Relevance to the Current Literature**

The results of the present study evaluating the predictive value of presurgical depression on anesthetic sensitivity have great implications and relevance to the current literature. Anxiety and depression have been previously shown to affect anesthetic responsiveness. One study showed that patients with higher preoperative anxiety required more intraoperative anesthetic than patients with lower baseline preoperative anxiety (Maranets & Kain, 1999). A meta-analysis (Dickens, McGowan & Dale, 2003) examining the impact of patient depression on experimental pain perception suggests that depressed patients may have a lower threshold for pain than non-depressed patients, and therefore require increased doses of anesthetic drugs to compensate for that effect. Nonetheless, these studies have been limited in scope; namely, they have not addressed the independent impact of depression on anesthetic response.

Other lines of research have, however, laid the foundation for the current investigation, which proposes a model linking depression and anesthetic sensitivity via the conceptual framework of the literature linking depression to asymmetrical activation of the frontal cortex. To resummarize, general anesthesia results in suppression of frontal lobe activity, a process that has been referred to as “depth of anesthesia” (Bruhn et al., 2006), or anesthetic depth. Previous research has shown that greater anesthetic depth may be a clinically important predictor of increased incidence of 1-year mortality among non-cardiac surgical patients (Monk et al., 2005). However, there is little research on the predictors of anesthetic depth. It has been hypothesized
that patients who have less physiologic reserve may be more susceptible to the depressant effects of anesthesia (Muravchick, 1998), and may therefore experience greater anesthetic depth and possibly greater anesthesia-related outcomes. Premorbid patient factors that are associated with suppressed frontal lobe activity may heighten risk for greater anesthetic depth. Depression, for example, has previously been associated with reduced frontal activity (e.g., Davidson, 1998). Therefore, depression may compromise reserve and heighten risk for greater anesthetic depth among individuals undergoing surgery; hence, the strength of the present study.

Results from the primary aim of the current investigation partially support the role of depression in response to anesthesia. Indeed, it is possible that there are other factors that may mediate the relationship between anesthetic sensitivity and adverse intraoperative and postoperative outcomes. However, depression can negatively impact at-risk individuals by increasing risk for or complicating the course of cancer and its treatment and even speeding the progression of the disease (Katon & Sullivan, 1990). As the results of the primary aim indicate, in order to adequately assess the relationship between stressful life events (conceptualized as the combination of physical, environmental, emotional, and psychosocial variables), physiologic/cognitive reserve, and prognosis, depression should be routinely considered as a marker of increased vulnerability. Considering the prevalence and impact of depression on patients with gynecologic tumors, including those with imminent cancer diagnoses, as well as the sensitivity of the MBMD in detecting depression in medical populations, the current study is an important and necessary addition to our clinical knowledge and practice. Specifically, it has vast implications for interventions that consider depressive symptoms in presurgical assessments.

**Limitations of the Present Study**

Several methodological limitations are noted for the present study. As previously mentioned, anesthetic sensitivity was measured using ‘area over the curve’ (AOC), a term
mathematically derived from the formula for ‘area under the curve’ (AUC), which is commonly used to measure physiological or endocrinological changes over time. Though this method is problematic in that calculations of AUC (or any derivative, such as AOC) have not been standardized (Pruessner et al., 2003), it was determined to be the best method to address the current hypothesis. Further, the examination of anesthetic sensitivity in relation to depression is relatively novel. In this case, ‘area over the curve’ (AOC) was calculated by subtracting ‘area under the curve with respect to ground’ (AUCG) from the total area. The rationale for using AOC rather than AUC, which essentially provides the same information with respect to changes in a physiologic phenomenon over time, related to ease of interpretation. Considering the difference between changes in response to anesthesia compared to changes in cortisol levels, for example, it seemed better to express findings as a positive relationship (e.g., higher depression scores are related to greater AOC estimates, or anesthetic sensitivity) as opposed to an inverse one (e.g., higher depression scores are related to lower AUC estimates).

Another issue in relation to using AOC estimates to measure anesthetic sensitivity is the limited number of events (i.e., records of Bispectral Index scores) used to calculate AOC; stated differently, the duration of time considered in the estimation of anesthetic sensitivity may have been to short to observe the desired effect. Individuals’ responsiveness to anesthesia was examined during the critical period defined as baseline to anesthetic maintenance, designated as 6.5 minutes post-anesthetic induction. While extending this period would provide a more accurate picture of anesthetic sensitivity, issues with variability in intraoperative factors, such as medications administered, patient homeostatic status, procedures performed, and complications, would likely confound our AOC estimates.
Also, use of BIS as an indicator of anesthetic depth has not been validated or established as the gold standard measure of anesthetic depth (Bruhn et al., 2006). Recall, BIS is a dimensionless EEG-derived value that utilizes a unilateral sensor (integrated from 3 or 4 electrodes) to obtain an electroencephalographic signal from the forehead (Bruhn et al., 2006). It differs from the traditional EEG in that it provides a single variable that is derived from several disparate descriptors of EEG (Bruhn et al., 2006). Though BIS is highly correlated with behavioral assessments of depth of anesthesia (e.g., anesthetic awareness), caution should be used when drawing conclusions about the ability of BIS to assess EEG waves. Specifically, caution should be used when using BIS to discriminate between depressed and non-depressed individuals on the basis of a correlation between depression and reduced frontal activity in the frontal cortex. This is particularly significant considering the research in this area has traditionally employed the use of traditional EEGs, which typically use more electrodes (as in an electrode cap). To provide a few examples, Reid, Duke and Allen (1998), Bruder and colleagues (1997), and Henriques and Davidson (1991) used 27, 30, and 14 electrode sites, respectively.

Whether depression increases risk for anesthesia-related complications by increasing sensitivity to anesthetic induction is still unknown. Though the relationship between depression and anesthetic sensitivity was partially supported, we are unable to assume causality from a correlational design. Further evaluation of this relationship is warranted. Indeed, a longitudinal design may help clarify the long-term impact of depression on surgical outcomes. Also, consideration of other potential covariates may be indicated.

Finally, to address a more operational limitation of the present study, the lack of significant findings for a relationship between depression and anesthetic sensitivity across all the measures
used, as well as the failure to detect group differences, may be limited by the small sample size. As previously mentioned, 17 of the 43 participants who consented to participate in additional psychological and neurocognitive testing (i.e., as part of their enrollment in the concurrent longitudinal study) were excluded from the current analysis. The primary reason for exclusion was invalid, inaccessible, or otherwise missing BIS data. Some systematic factors that may have contributed to the loss of this data are being considered. Indeed, the current analyses may have been enhanced by a larger sample. However, the current findings still highlight the need to identify patients at-risk for adverse intraoperative and postoperative outcomes, which may have vast implications for improving patient care before, during, and after surgical interventions.

**Directions for Future Research**

Again, results of the present study suggest that depression may be an important marker of anesthetic sensitivity. More research is needed to evaluate this relationship, as well as to identify other premorbid indices of risk for adverse outcomes. Some possibilities may include patients with reduced presurgical frontal function (e.g., as measured by neuropsychological assessment), dementia, mental retardation, or neurological damage (i.e., to the prefrontal cortex of the brain). In fact, there has been some research to suggest that reduced frontal-specific abilities, such as working memory and higher order problem solving, is associated with general cognitive slowing in these populations (Devenny et al., 2000; Jelic et al., 2000; Lindal, 1990; Numminen et al., 2001; and Sinanovic et al., 2005). Similar to studies linking depression to reduced frontal activity, these studies have, for the most part, used EEGs to ascertain these relationships.

Furthermore, there is a need to validate the research linking depression to neuroanatomical abnormalities in the frontal cortex of the brain in the present population. Confirming that depressed individuals are more susceptible to anesthetic effects because of their predisposition to
reduced frontal activity is an important addition to the current literature and a likely next step. This can be achieved by obtaining presurgical EEG profiles for each participant.

Additionally, the current findings suggest that future research could incorporate findings from research examining the physiological and neurological components of depression. For example, researchers might investigate the relationship between cortisol levels and depression, among other possible physiological or psychological stressors (e.g., stress, anxiety), and their combined impact on anesthetic sensitivity. This is based on previous research that has linked depression to dysregulated cortisol across populations, including cancer (Cohen et al., 2001; Sephton et al., 2000). Thus, examining the relationship between depression and cortisol in this sample may have significant implications for understanding how the two factors may moderate individuals’ anesthetic response.

**Summary and Conclusion**

In sum, the present study examined the relationship between depression and anesthetic sensitivity in a group of women, age 40 and older, undergoing surgery for the removal of gynecologic tumors. The first aim tested the hypothesis that depression severity, as assessed by four independent measures of depressed mood, would demonstrate greater sensitivity to initial anesthetic induction. Further, it was hypothesized that there would be group differences in anesthetic response, with women in the history of depressive symptomatology group demonstrating relatively more anesthetic sensitivity. Results provided some evidence for a relationship between depression severity and anesthetic sensitivity; however, the group difference hypothesis was not supported. One possible explanation for this discrepancy is that the depression-anesthetic sensitivity link is measure-specific. Specifically, the measures that were correlated with anesthetic sensitivity seem to be more sensitive to the assessment of current depressive symptomatology.
The present study is an important first step in examining premorbid factors that may influence anesthetic response, and thereby, contribute to adverse intraoperative and postoperative outcomes. From the literature, it is clear that examination of risk factors such as depression may be useful in identifying individuals who are at increased risk for negative outcomes associated with anesthesia. Although correlational analyses will not provide causal evidence for the relationship between depression and anesthetic sensitivity, the current study represents a significant movement towards identifying areas for clinical intervention at the preoperative, intraoperative, and postoperative levels. For example, the MBMD Depression Scale, one of the measures that demonstrated sensitivity to identifying individuals at increased risk for negative anesthetic response, is an invaluable assessment tool that has vast implications for moderating factors that may complicate or undermine treatment efforts. Needless to say, the current study emphasizes the need for interdisciplinary efforts in prevention and intervention in this patient population.


BIOGRAPHICAL SKETCH

Rachel André was born and raised in Miami, FL. She is a Phi Beta Kappa graduate of Howard University in Washington, D.C., where she earned a Bachelor of Science in psychology. Her minor area of concentration was chemistry. Ms. André is currently pursuing her doctorate in clinical psychology at the University of Florida, specializing in health psychology. Current clinical and research interests are in the area of obesity research and treatment, culture and body image, as well as the psychosocial impact of health problems at the individual and community levels. Areas of particular interest to Ms. André are those that have vast public health implications (e.g., sexually transmitted diseases such as HIV/AIDS and HPV; obesity).