The Speechless Brain

behavioral studies of
memory and emotion
during anesthesia

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Sprakeloze hersenen

gedragsstudies van
geheugen en emotie
tijdens anesthesie

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When I remember back to this time in the hole, I can't really remember what happened to me while I was in it. I can't remember what I really felt. Maybe nothing happened, maybe these emotions I remember are not the right emotions. I know the others came and got me out after a while, and the game or some other game continued. I have no image of myself in the hole; only a black square filled with nothing, a square like a door. Perhaps the square is empty; perhaps it's only a marker, a time marker that separates the time before it from the time after. The point at which I lost power.

Elaine in *cat's eye* (Margaret Atwood, 1990)

Preface

This thesis is not about Consciousness, Memory or Emotion. All three concepts have given rise to a great deal of speculation and remain subject to vivid discussion. This thesis entails an empirical exploration, however, not a theoretical one. Studies were designed to investigate human information processing during anesthesia using a memory and affective priming paradigm, and as such, this thesis deals with an altered state of consciousness, with memory and with emotion.

Consciousness is an elusive concept (Tassi & Muzet, 2001) that boils down to the mind-body problem which revolves around the question what the nature of our mental states and processes is. Are mind and brain two distinct phenomena, the former being nonphysical as opposed to the latter being physical (dualistic approach) or are both biological entities legitimate to be studied empirically (reductionist approach)? This classical issue continues to intrigue many. David Chalmers, an influential philosopher and cognitive scientist of today, distinguishes between "easy problems" and the "hard problem" of consciousness (Chalmers, 1995). Easy problems are associated with consciousness yet all concern objective mechanisms of the conscious system. These problems are likely to be solved with continued work in cognitive psychology and neuroscience. The hard problem, however, pertains to the question of how physical processes in the brain give rise to subjective experience. According to Chalmers, this problem poses the real mystery of the mind. For empirical purposes, consciousness is denoted as *phenomenal awareness* (Bosinelli, 1995), a mental state that allows us to report what goes on or is felt at a specific point in time. When anesthetic drugs are administered, people ultimately lose reportability, and so to speak, consciousness is lost.

Although we have come to think of ourselves as rational human beings exerting control, “life is what happens while you're busy making other plans” (Lennon, 1980). As will be argued in chapter 2, human and animal behavior is profoundly affected by emotion. How emotions come about and what they are, scientists do not agree upon. Some theories tend to explain emotions in terms of cognitive processes, an emotion not being different from cognition, a thought. Thereby, cognitive theories have turned emotions into cold, lifeless states of mind (LeDoux, 1998, chap. 3). There is abundant behavioral and neurological evidence, on the other hand, that emotional behavior is dissociated from normal thought processes and largely arises unconsciously. This provided the basis for investigating emotional information processing during general anesthesia in this thesis. The myriad of physiological, behavioral and subjective phenomena typically associated with "emotion" or "emotional" are beyond the scope of this thesis and reviews may be found elsewhere (e.g., Frijda, 1988). For present purposes, emotions are viewed as biological function of the nervous system (LeDoux, 1998, chap. 1; Zajonc, 1980). They are presumed to be vital to human and animal information processing, and to arise with minimal stimulus input and cognitive requirements. As such, emotional responses may be expected to occur during general anesthesia as well. The arguments for this position are provided in chapter 1.

The concept of memory touches on the mind-body problem but is more distinctly hotly debated for its cognitive architecture. Many psychological models of memory distinguish between short-term (primary) and long-term (secondary) memory stores. Short-term memory refers to the transient contents of conscious mental activity, whereas long-term memory is conceived as a larger store containing information that faded from consciousness over a period from a few minutes to a lifetime. The controversy evolves around the organization of long-term memory (Foster & Jelicic, 1999). Based on studies of preserved and impaired memory performance following brain damage, most neuropsychologists tend to think of memory as comprising multiple independent, empirically separable systems (structural approach). The majority of cognitive psychologists, on the other hand, conceive of memory as a processing framework that can be tapped via different levels (functional approach). System theorists hold the nature of brain damage responsible for the pattern of memory impairment whereas processing theorists regard the nature of cognitive processing critical to the constellation of findings observed in memory experiments. As Endel Tulving recently pointed out, "the debate is to a large extent a conceptual one . . . that appears to be revolving around interpretations of facts and explanations of phenomena" (Tulving, 2000, pp. 41-42). This thesis has no intention to argue in favor of either conception of memory, albeit that the terminology used and background of the author suggest otherwise.

For future purposes, and in line with current notions in the literature, a clear distinction is made between expressions of memory on the one hand and the processes giving rise to such expressions on the other. The latter may also be referred to as information processing, memory function, or learning, although learning implies formation of a new association, which was not necessarily attempted in this thesis. Evidently, processes and expressions may be separated in time, as is clearly the case in the current investigation in which participants (surgical patients) were presented with stimulus material during anesthesia, and tested for memory a few hours later postoperatively. The point is that whereas both processes and expressions may be conscious or unconscious, the two are not necessarily related. Unconscious expressions of memory may arise from a conscious process and vice versa. Thus, when one attempts to unravel the nature of processing based on memory test performance, confusion easily arises and faulty conclusions are likely to be drawn. The situation is further aggravated by the lack of an objective measure of consciousness, or conscious information processing for that matter (taking reportability as evidence merely reflects a practical point of view rather than a theoretical one). Had such a measure existed, the distinction (and current investigation) would have been superfluous. These matters are discussed more detailed in the introduction.

Aims

This thesis describes investigations into memory function in surgical patients under anesthesia. In a worst case scenario, sleep (hypnosis) is insufficiently induced and/or maintained and the patient regains consciousness, is aware of surgery and possibly in pain. Such an experience is often traumatic and may have devastating, long-term psychological consequences. Ideally, anesthesia induces unconsciousness and recollection of intraoperative events is lost. The latter scenario provided the research setting for this thesis, which specifically addresses two questions:

1) Does memory function depend on hypnotic adequacy?
2) Does memory function depend on the type of information?

Outline

Studies were conducted in healthy, ambulatory patients scheduled for relatively short elective surgical procedures under general anesthesia. In all cases, anesthesia was induced and maintained with propofol, an intravenous anesthetic with favorable clinical and pharmacodynamic properties for this type of patient and surgery. Novel psychological and neurophysiological techniques were combined to assess memory function during two levels of anesthesia: adequate hypnosis and deep sedation. Each level was examined in separate studies, as was the effect of non-emotional and emotional information. Both the influence of hypnotic state and type of information on memory function (2 × 2 factorial design) were addressed, and four experiments were conducted.

The first chapter introduces behavioral studies of memory and emotion in general, and during anesthesia in particular. Part one provides a background to memory assessment and reviews recent technological developments in monitoring hypnotic state during anesthesia. Part two briefly reviews human and animal responses to emotional stimuli, and describes the neurobiological basis of emotion. The chapters that follow report on the experiments that were conducted to address the aims of this thesis. With the use of a memory priming paradigm with relatively familiar Dutch words, chapters 2 and 3 describe investigations into memory function during adequate hypnosis and deep sedation, respectively. In chapter 3, individual differences in memory function are addressed as well. Chapter 4 highlights patient awareness that was observed during deep sedation from a phenomenological and neurophysiological point of view, and describes its relation to postoperative conscious recall. Chapter 5 investigates processing of emotional information and its effect on memory function during adequate hypnosis. A similar paradigm is adhered to during deep sedation, which is reported on in chapter 6. In chapter 7, finally, the main findings and conclusions of the studies presented in this thesis are discussed.

1 General introduction

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Part I: Memory

Fundamentals of memory

The study of memory is closely related to the study of learning and arose from philosophical questions about how people come to know things. Complex ideas are allegedly formed in mind by connecting simple ideas based on sensations that are experienced contiguously in time and/or space (association by contiguity). In previous centuries, philosophers speculated about factors affecting the degree or strength of associations. It was recognized that associations would vary according to the vividness of the original experience, its duration, its frequency, and its interest to the observer. Retrieval from memory was hypothesized to vary with the resemblance of the stimulating cue to memory, the recency of the experience, and the coexistence of alternative associates to the cue (Bower, 2000). Many learning theories of today deal with these factors in some way. Ebbinghaus (1850-1909), a German psychologist, pioneered in the scientific study of association formation using controlled systematic experiments with himself as the sole subject. His observations and methods of investigation set the stage for human memory research in the twentieth century.

A concise review of research (Bower, 2000) demonstrates what our ancestors already suspected:

- Increasing the number of study trials and study time per item increases learning and retention
- Stimulus familiarity and meaningfulness facilitate learning
- New material will be remembered more easily the less complex it is
- Performance improves rapidly at first but then increasingly slowly as practice proceeds
- Less attention and cognitive effort are required as practice proceeds
- Similarity between items improves recall but also creates confusion errors
- Preexisting associations can create intrusions before the correct, novel association wins out
- Recognition tests are easier than recall tests and more sensitive to small differences among weak associations
- Forgetting occurs rapidly at first (hours, days) and more gradually thereafter
- Forgetting results from autonomous decay and interference from other associations
- Access to memory requires a stimulus during test to arouse the same as it did during study

If one is simply interested in the retention of study items, as in this thesis, these notions provide important clues for the to-be-used memory paradigm: the study material should repeatedly be presented and not be too complex and novel, or else learning and memory are unlikely to occur; nor should items be too familiar lest existing associations interfere with memory; the items should be distinct from one another to prevent confusion at test;

memory should be tested at the earliest convenient time, and ideally, the conditions during study are reinstated at test.

Measures of memory

Memory is commonly associated with conscious retrieval of information or experiences. Traditional memory tests –free recall, cued recall, recognition tests– rely on conscious recollection indeed by making explicit reference to a learning episode or prior experience. In free recall tasks, for instance, subjects simply report what they remember, in any order they like. Subjects may also be presented with cues in order to trigger memory (cued recall). In recognition tests, subjects judge whether or not a particular item was part of the material studied earlier. Because instructions explicitly refer to an episode in the subject's personal history, such tasks are referred to as *direct* or *explicit* tests of memory. Others have used labels like autobiographical, episodic or intentional to refer to this type of test (Richardson-Klavehn & Bjork, 1988).

Task performance may also be influenced by a prior experience without conscious recollection of the event, however. Previous exposure to test stimuli generally increases the accuracy of correct responding at test and decreases response latency, a phenomenon referred to as *direct* or *repetition priming*. Similarly, prior exposure increases the probability of those items being generated at test. When study material is not identical to the test material but relates to it in some (conceptual, semantic, phonemic, graphic) way, changes in subsequent test performance are referred to as *indirect priming* effects. Priming effects have been demonstrated in normal and memory-disordered (amnesic) subjects for conceptual, factual, lexical, perceptual, and procedural knowledge (Richardson-Klavehn & Bjork, 1988), and provided the basis for recognizing memory manifestations other than conscious recollection. Graf and Schacter (1985) introduced the terms *explicit* and *implicit* memory to discriminate between conscious recollection on the one hand and memory manifestations other than conscious recollection on the other. The evidence for such a distinction is compelling (Kihlstrom, 1987; Schacter, 1987; Schacter, Chiu & Ochsner, 1993).

Because direct memory tests heavily rely on conscious recall, priming is commonly associated with a different set of tasks that make no reference to the learning episode but are nonetheless influenced by it. Such tasks are referred to as *indirect* or *implicit* measures of memory (Richardson-Klavehn & Bjork, 1988). For instance, subjects may be asked to generate associates to a test stimulus, to decide whether or not a briefly presented stimulus is a word, to identify degraded stimuli, to complete word stems (i.e., first few letters of a word) or word fragments to words, to spell auditorily presented homophones, or to make some form of evaluative judgment. Neurophysiological indices, like event related potentials, galvanic skin- and conditioned responses, may also be included as indirect measures of memory. Rather than directing the subject to a particular target event or piece of information in his or her personal history, indirect measures assess behavioral change due to prior exposure or experience. Evidence of memory is revealed by comparing performance with relevant prior exposure to performance without such exposure, and hence, is derived by comparing separate data points (Richardson-Klavehn & Bjork, 1988).

Using both direct and indirect measures of memory, studies revealed striking dissociations in performance (Richardson-Klavehn & Bjork, 1988; Roediger, 1990). Amnesic subjects, for instance, generally show preserved memory on indirect tests but perform poorly on direct tests as compared to control subjects who do not suffer from amnesic syndromes. This pattern of results has been found with a variety of indirect tasks testing retention of semantic, lexical and procedural knowledge (Richardson-Klavehn & Bjork, 1988). In normal subjects, manipulations during study (encoding) of material, such as elaborate versus superficial study or study time, strongly influence performance on direct tests but do not so much affect the amount of priming observed with indirect tests. Changes in the modality of stimulus presentation during study and test, on the other hand, typically attenuate performance on indirect tests but are less important to direct test performance. Such dissociations across measures supported the notion that direct and indirect tests tap different forms of memory ("Transparency"), or even different memory systems. Whereas direct tests supposedly measured conscious processes, indirect tests were assumed to index priming or unconscious processes. Using a task-comparison methodology, Richardson-Klavehn and Bjork (1988) reviewed dissociations, parallel effects and complex patterns of differences and similarities across direct and indirect measures of memory, varying systematically with critical variables. Beside dissociations, they described a number of parallel effects and complex patterns across measures that could not well be explained in terms of testing methodology. Their review demonstrated that the direct/indirect distinction poorly predicted dissociations and nondissociations. Instead of taking test performance as evidence of either conscious or unconscious processing, the authors stated that dissociations between direct and indirect memory tests only permit to conclude that the two types of tests reveal different aspects of memory function, and summarized to say that "memory is multifaceted and highly versatile".

A similar discussion haunted the study of perception where a dissociation paradigm was frequently used to demonstrate perception without awareness. In this particular area of research, Reingold and Merikle (1988) subscribed to the appeal of the dissociation paradigm using one measure to indicate the availability of conscious stimulus information, and another to indicate availability of information regardless of its availability to conscious awareness. Beside the controversy over what constituted an adequate behavioral measure of conscious experience (Merikle, 1992), Reingold and Merikle (1988) noted that investigators often relied on two questionable assumptions when using the dissociation paradigm. First, a direct measure of perception, such as reportability, could not be assumed to index conscious processes exclusively and to be never influenced by unconscious processes (Exclusiveness assumption). Secondly, it could not be assumed that the direct measure was sensitive to all conscious stimulus effects for this implied that the measure provided an exhaustive index of conscious processing (Exhaustiveness assumption). To resolve some of the issues, Reingold and Merikle proposed to compare the relative sensitivity of direct and indirect measures to conscious information under comparable experimental conditions. According to their notion, unconscious perception was demonstrated whenever an indirect measure showed greater absolute sensitivity to a particular stimulus dimension than a comparable direct measure. This approach was advocated in memory research as well and found to support claims of unconscious memory (Merikle & Reingold, 1991).

The controversy over unconscious memory and perception did not reside, however. Shanks and St John (1994), for instance, argued that was it impossible to establish whether a dissociation is genuine or merely reflects inadequate sensitivity and relevance of a direct measure to conscious information processing. Moreover, they evaluated, studies with stimuli rendered unavailable to conscious awareness due to very brief (subliminal) exposure durations, yielded unconvincing evidence of unconscious perception and learning. It was extremely difficult to establish that stimuli were indeed presented below the threshold of conscious perception (Holender, 1986). Inspite of their caution, Shanks and St John (1994) concluded there was substantial evidence for more than one conscious learning strategy and knowledge type. What constituted this other class, the authors did not elucidate.

The process dissociation procedure (PDP)

In yet another field of research, the study of attention, Jacoby (1991) noted that investigations of memory, perception and attention all faced the same problems. Foremost, studies relied too much on a one-to-one mapping between processes and tasks, whereas a result taken as evidence of an unconscious influence could have arisen from a conscious use of memory or perception that was undetected by the experimenter. Although this had already been noted by others, as described in the preceding section, Jacoby proposed a process-oriented instead of task-oriented approach, and accordingly introduced a methodological framework, the process dissociation procedure. In his 1991 article, Jacoby set out to recognize that the difference between direct and indirect tests could be described in terms of intentional versus automatic processing, two central concepts in theories of attention. These theories identify consciousness with a central, limited-capacity system that controls mental processing. Intentional processing, on the one hand, is consciously controlled and subject to attentional capacity limitations, whereas automatic processing occurs as a passive consequence of stimulation that is not necessarily accompanied by awareness, and which requires neither intention nor processing capacity. Jacoby emphasized there was not a one-to-one mapping between these processes and tasks: conscious processes could affect ("contaminate") performance on an indirect test and direct test performance could be affected by unconscious processing. The question is how to separate the two.

PDP relies on the observation that unconscious processes may serve as a source of both facilitation and of interference. Feelings of familiarity may improve recognition judgments but may also cause errors (false recognition). Warrington and Weiskrantz (1968), for instance, in studies with amnesics, observed intrusions in recognition performance from word lists that had been learned on earlier days (i.e., proactive interference). They demonstrated more or less accidentally that amnesics were able to store information. Intentional processing, on the other hand, serves the purpose of performing well and to respond correctly on the task at hand, opposing errors, slips, and to-be-ignored information. In two experiments, Jacoby (1991) investigated the effect of divided versus full attention at test on facilitation and interference of recognition judgments. The idea was that divided, as opposed to full, attention greatly reduces consciously controlled processing, leaving automatic influences of memory unopposed and invariant. Conscious and unconscious influences of memory were thus defined in terms of their reliance on processing capacity, i.e., on attentional resources during test. In the first experiment (a facilitation paradigm), correct recognition was higher under full than under divided attention but only when words had been studied elaborately. This led Jacoby to conclude that intentional uses of memory, in contrast to automatic influences, depend on the level of processing during study and the availability of attentional resources. In the second experiment (an interference paradigm), false recognition was higher during divided attention, in particular for words that were studied elaborately. This confirmed the notion that limited attention impaired conscious uses of memory but not automatic influences, leaving performance errors in the second experiment unopposed.

A third experiment, introducing the process dissociation procedure, was devised to separate the contributions of automatic and intentional uses of memory to recognition performance. To do so, Jacoby (1991) combined data from a facilitation and an interference paradigm. As the previous experiments had shown, consciously controlled responding enables people to respond differentially depending on the demands of the task at hand. It allows them to *select for* items presented earlier (e.g., first experiment) or to *select against* such items (e.g., second experiment). Automatic influences of memory, in contrast, do not support such selective responding and are relatively invariant. Given that only one process varies with task demands, the contributions of both can be inferred from performance under two test conditions: one in which unconscious and conscious influences act in concert and both facilitate performance, and one condition in which the two act in opposition. Jacoby referred to these as the inclusion and exclusion test conditions, respectively. In the inclusion condition, subjects were instructed to use information studied earlier, whereas such information was to be avoided in the exclusion condition. Having participants perform under both conditions, conscious control could be measured as the difference between performance when people are *trying to* as compared to when they are *trying not to*, hence, by comparing the two test conditions. From this, using simple algebra, the contribution of unconscious influences to test performance could be estimated. Jacoby validated his procedure and compared estimates of automatic uses of memory in the last experiment with observed probabilities of recognition memory during divided attention in experiment 2. The fit was near perfect.

Jacoby (1991) originally applied the PDP to recognition memory judgments and manipulated attention during memory testing. In subsequent studies, the procedure was used in combination with cued recall (word stem completion) tasks and a number of variables, like full versus divided attention during study, have been investigated for their effects on conscious and unconscious influences of memory (Hay & Jacoby, 1996; Jacoby 1998; Jacoby, Toth & Yonelinas, 1993). The overall pattern was consistent: unconscious influences remained invariant across manipulations of attention that substantially reduced conscious influences. Others adopted the paradigm as well and recognized its importance as an empirical, methodological tool to separate conscious and unconscious bases of responding within one task. Clearly, the PDP addressed a major issue in the study of consciousness and memory. There has been criticism as well, not so much as casting doubt on the rationale underlying the PDP, but on the estimation of unconscious influences. The PDP requires a model specifying the relation between conscious and unconscious processes. Whereas Jacoby and colleagues assumed and argued in favor of independence (Jacoby, Toth, Yonelinas & Debner, 1994), alternative relations have been proposed, affecting the magnitude and "invariance" of unconscious influences (Joordens & Merikle, 1993). The discussion over the merits of alternative models continues (Stolz & Merikle, 2000). Furthermore, the process dissociation framework was shown to ignore guessing, a response bias that potentially affected all parameters in the PDP (Buchner, Erdfelder & Vaterrodt-Plünnecke, 1995). This led Buchner, Erdfelder & Vaterrodt-Plünnecke (1995) to conclude that, though invaluable, the process dissociation framework did not guarantee process-pure measurement of conscious and unconscious processes. Jacoby and colleagues advocated the use of PDP as a tool to identify factors that selectively influence the two forms of processing (Jacoby et al., 1993).

In summary

Memory research has a long tradition in psychology. Beside explicit (conscious) memory, implicit (unconscious) memory is distinguished, referring to the notion that memory may reveal itself in the absence of conscious recollection. The presence or absence of conscious recollection, however, cannot be taken as evidence of either conscious or unconscious processing. Rather, memory should be considered a blend of conscious and unconscious processes that both contribute to performance on a particular task, be it a direct or indirect test. The two may be separated within one task using the process dissociation procedure. The previous section illustrated the complexity of assessing memory and inferring from this what lies beneath. This bears particular relevance to clinical studies of memory function during anesthesia, which will be discussed next.

Memory during anesthesia

Traditionally, memory for surgery is assessed by asking patients whether they remember anything from the intraoperative period. Patients hardly ever recollect surgical events, with the exception of those who suffered "awareness". Oddly enough, the generally accepted meaning of awareness during anesthesia is such that explicit memory exists for events during the period of intended anesthesia (Vernon & Sebel, 1993). Hence, awareness and conscious recall are treated alike. As we have just seen and as will be shown shortly, this interpretation of awareness is problematic. Nevertheless, the incidence of conscious recall after anesthesia with current anesthetic agents and techniques approximates 0.1% (Liu, Thorp, Graham & Aitkenhead, 1991; Sandin, Enlund, Samuelsson & Lennmarken, 2000). Higher incidences have been reported when a limited amount of anesthetic has had to be given, such as during cardiac, obstetric and trauma surgery, and when neuromuscular blocking agents are used. Such drugs induce paralysis, which reduces anesthetic requirements and supports a smooth surgical procedure. When given in combination with too few hypnotic (sleep) and analgesic (painkiller) agents, however, the patient regains consciousness and experiences pain, yet is unable to move. Such awake-paralysis denotes a particularly stressful event even when no pain is experienced (Moerman, Bonke & Oosting, 1993). Clearly, such events are remembered.

Fortunately, conscious recall is absent in the majority of surgical patients. This has been, and still is, erroneously taken as evidence that patients do not regain consciousness or process information during anesthesia. The error is dramatically illustrated by studies assessing awareness intraoperatively by instructing patients to squeeze or open and close the fingers of their hand. Because neuromuscular blocking drugs are often used, such studies relied on a specific procedure referred to as the isolated forearm technique (IFT). Tunstall who used the IFT in women undergoing cesarean section introduced the technique in 1977 (Tunstall, 1977). By inflating a pneumatic cuff around the patient's arm (to 200 - 250 mmHg) before administering blocking drugs, the anesthesiologist using the IFT prevents the hand from being paralyzed and fingers may be moved spontaneously or upon request. Studies have shown that patients may respond to command in the absence of conscious recall (Bogod, Orton, Yau & Oh, 1990; Byers & Muir, 1997; Flaishon, Windsor, Sigl & Sebel, 1997; Gaitini, Vaida, Collins, Somri & Sabo, 1995; King, Ashley, Brathwaite, Decayette & Wooten, 1993; Millar & Watkinson, 1983; Russell, 1993; Russell & Wang, 2001; St Pierre, Landsleitner, Schwilden & Schuettler, 2000; Thornton, Barrowcliffe et al., 1989). These studies with the IFT illustrate how the incidence of awareness and information processing in surgical patients may be underestimated when conscious recall is taken as evidence.

The notion of implicit memory, officially introduced in 1985 (Graf & Schacter, 1985), was readily adopted in research during anesthesia. Two decades earlier, Levinson (1965) had already noted that patients could retain memories of a mock crisis induced during anesthesia, other than conscious recall. He used hypnosis to regress patients to the actual operation and observed accurate memory for the event in four out of ten patients and partial memory in another four. Some investigators caught up on the possibility of residual memory function and auditory information processing during anesthesia (e.g., Bonke, Schmitz, Verhage & Zwaveling, 1986; Dubovsky & Trustman, 1976; Eich, Reeves & Katz, 1985; Millar & Watkinson, 1983; Standen, Hain & Hosker, 1987; Stolzy, Couture & Edmonds, 1987). The renewed interest in the psychological unconscious that awoke in the 1980s boosted investigations under anesthesia. More important, sound methodologies (including control groups) and a variety of tests were adopted. In a typical experiment, patients are presented with verbal material during anesthesia, usually shortly after induction of anesthesia or first surgical incision. Postoperatively, conscious recall is assessed with a short structured interview (e.g., Liu et al., 1991) and patients may complete a recognition task. Beside such direct testing methods, an indirect task is usually administered in which material presented under anesthesia can be used. Memory is evident when responses are influenced or dominated by the intraoperatively presented material. In the absence of conscious recall, this establishes evidence of implicit memory. Reviews of studies may be found elsewhere (Andrade, 1995; Ghoneim & Block, 1992; Ghoneim & Block, 1997; Kihlstrom & Couture, 1992).

A confusing pattern of positive and negative results emerged. Merikle and Daneman (1996) therefore conducted a meta-analysis on the data from 1492 patients (in 29 studies) in whom memory for specific information presented during anesthesia had been assessed with direct and indirect tests of memory. The results, published in 1996, were clear and indicated a reliable implicit memory effect, as long as testing is not delayed for a period of more than 36 h. The overall average effect size (product-moment correlation coefficient, r) was significant when memory had been tested either less than 12 h following surgery (r = 0.23) or between 12 and 36 h postoperatively (r = 0.10). Moreover, the meta-analysis indicated that both direct and indirect tests could reveal implicit memory for material presented during anesthesia. Merikle and Daneman concluded that results did not support the assumption that indirect test were more sensitive tests of implicit memory than direct tests. This meta-analysis is clinically significant in the sense that it is no longer acceptable to assume that patients' inability to remember surgical events, means that information has not been processed to some degree and remains available in memory to influence experience, thought and action.

Despite the evidence of reliable implicit memory, the question to what extent information could be processed during *adequate* anesthesia was an open one. Many, if not most, anesthesiologists have rejected this possibility at the outset on the grounds that adequately anesthetized patients are unconscious *by definition* (Kihlstrom & Couture, 1992). Implicit memory was simply impossible unless patients were inadequately anesthetized. This response ignored the concept of information processing outside conscious awareness. Moreover, it is generally recognized that our knowledge of the mechanisms underlying anesthesia is incomplete (Kihlstrom & Couture, 1992). Because implicit memory did not guarantee unconscious information processing, proponents of the residual-memory-function idea were left empty handed in the discussion. Strictly speaking, their case was just as fragile as that of the opponents and both parties lacked valid tools to support their argument. In order to find convincing evidence of *un*conscious memory function, therefore, Bonebakker and colleagues (Bonebakker, Jelicic, Passchier & Bonke, 1996) recommended new studies to pay attention to the best possible assessment of anesthetic adequacy. They themselves were the first to use the PDP in this field of research and demonstrated strong evidence of unconsciously mediated memory for words presented during balanced anesthesia, as revealed by an inability of patients to exclude such words in a postoperative word stem completion task (Bonebakker, Bonke et al., 1996). Hypnotic state during word presentation was, however, not monitored in these first exciting studies with the PDP.

Monitoring hypnotic state

Modern ("balanced") anesthesia typically comprises a combination of drugs: an anesthetic or hypnotic agent that induces loss of consciousness, an analgesic to reduce pain, and a muscle relaxant to induce temporary paralysis. Anesthetic potency is generally conceptualized in terms of patient movement. For inhalation anesthetics, for instance, the Minimum Alveolar Concentration (MAC) required to prevent movement in response to surgery in 50% of subjects (1 MAC) and 99% of subjects (1.1 MAC), provides an important reference model. Because movement may reflect spinal rather than cortical activity, the concept of MAC is not necessarily useful for monitoring conscious awareness. A similar argument applies to activity of the autonomic nervous system (ANS) which is traditionally and commonly used to signal awareness. Hemodynamic, respiratory, muscular and autonomic variables do not necessarily respond to changes in cognitive function, however, and have been discarded as reliable indicators of hypnotic adequacy (Schneider & Sebel, 1997). As the brain is the effect site of general anesthetics, the electroencephalogram (EEG) recently enjoyed renewed interest as a clinical monitoring tool of central nervous system (CNS) functional suppression during anesthesia and sedation (Rampil, 1998). The EEG is a complex signal representing electrical activity of the cerebral cortex. It is a largely randomly appearing signal with no obvious repetitive pattern or shapes correlating with particular underlying events. The waveform itself, therefore, is of little diagnostic value. The state of the brain is reflected in some statistical attributes of the EEG, such as the degree of synchrony in neuronal firing of cortical, pyramidal cells. This statistical approach lies at the heart of EEG monitoring for anesthesia-related purposes (Rampil, 1998; Sigl & Chamoun, 1994).

BIS monitoring technology

The EEG is an alternating voltage composed of many waveforms. After raw EEG has been acquired, the analogue signal may be translated into its digital counterpart for further analysis. Voltage changes over time can be examined, which is referred to as analysis in the time domain (Rampil, 1998). Frequency domain analysis, by contrast, examines signal activity as a function of frequency and evolves around the study of sine waves. These are simple mathematical functions defined by three basic elements: *amplitude* – one half the peak-to-peak voltage (µV), *frequency* – the number of cycles per second (Hz), and *phase angle*, reflecting the waveform's starting point relative to time zero. A typical sine wave starts at time 0 with amplitude 0. Any deviation from this typical starting point can be expressed, in degrees between 0° and 360°, as the fraction of a full cycle that the sinusoid shifts in time (Figure 1). Any complex time-varying signal may be decomposed into its sine wave components (Figure 2) and converted into a representation of frequency and amplitude, referred to as a Fourier transform. The resulting power spectrum comprises a series of discrete values corresponding to a particular frequency component and its power (V^2).

Various parameters have been derived from the power spectrum to indicate anesthetic depth. Frequency bands –delta, theta, alpha, beta frequency– are traditionally discerned and corresponding power values (i.e., band power) have been related to psychophysiologic state. Band power analysis is of limited utility because the bands have been defined for the activity of the awake or natural EEG without taking the altered nature of activity during anesthesia into account (Rampil, 1998). The frequency below which 50%

and 95% of the power in the EEG resides may also be derived, referred to as median frequency (MF) and spectral edge frequency (SEF), respectively. Power variables suffer several problems, however. They are sensitive to specific EEG patterns induced by different drugs (Rampil, 1998) and may show biphasic responses to certain anesthetics (Katoh, Suzuki & Ikeda, 1998). In addition, anesthesia-induced burst suppression (i.e., alternating periods of normal to high voltage activity changing to low voltage or isoelectricity) is problematic for spectral analysis (Billard, Gambus, Chamoun, Stanski & Shafer, 1997), and spectral analysis cannot quantify the amount of phase coupling in the EEG.

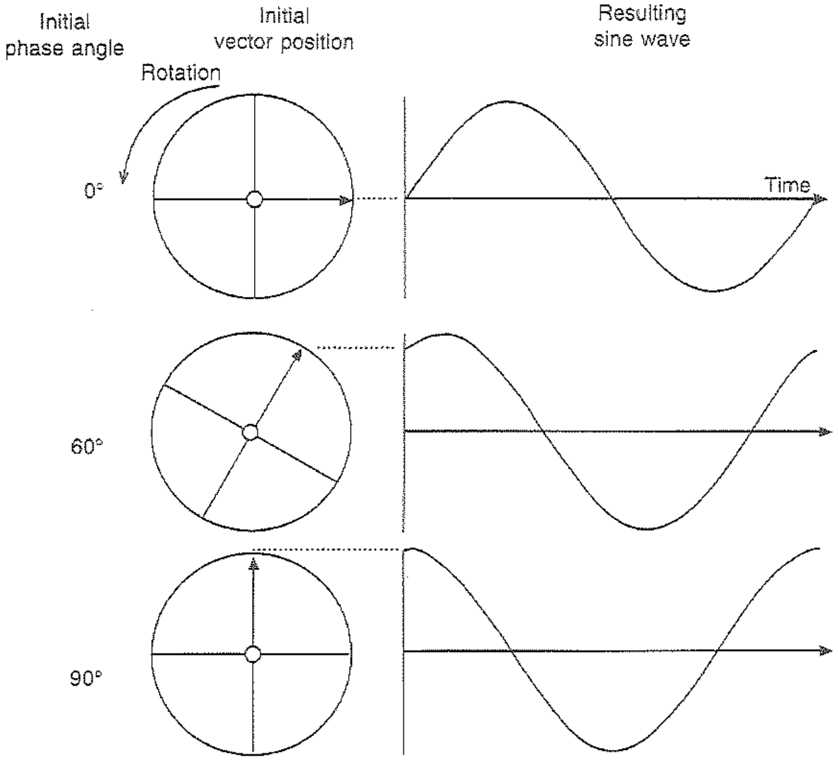

Figure 1. A rotating vector or spoke describes a sinusoid over time. In this example, imagine a wheel rotating counterclockwise with a light source in its rim adjacent to the marked spoke. As the wheel turns, a graph of the vertical position of the light versus time will produce the indicated sine wave. The rotational speed of the wheel determines the frequency of the resulting sine wave, and the size of the wheel determines its amplitude. The initial angle of the spoke is the phase angle of the sine wave. In this illustration, the wheel starts at three different phase angles. Note that the sine wave frequency is independent of the phase angle (Reprinted with permission from Rampil, 1998)

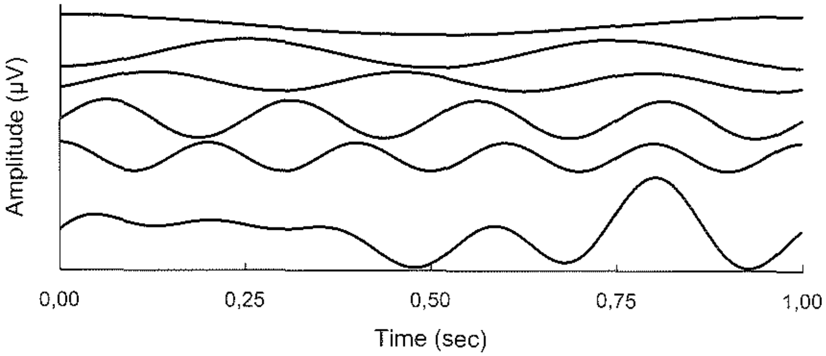

Figure 2. The upper five traces are five sine wave components (1,2,3,4, and 5 Hz) with respective amplitudes of 1, 1.5, 1,2, and 1.5 µV. The components have different offsets for illustrative purposes only. At the bottom is the sum of the five components. (Reprinted with permission from Sigl & Chamoun, 1994)

Phase coupling is an important characteristic of nonlinear systems like the brain (Sigl & Chamoun, 1994) and refers to interfrequency dependency. Frequency relationships may be examined with bispectral analysis of the EEG, which assesses phase correlations between different frequency components, and quantifies their bicoherence and joint magnitude. Hence, both phase and power information is incorporated in this type of analysis. Although the physiologic meaning of phase relationships remains unclear, strong phase coupling may imply that two components have a common generator or that the neural circuitry they drive may synthesize a new dependent component (Rampil, 1998). For clinical purposes, a single parameter has been developed, the bispectral index (BIS), incorporating a set of EEG features each chosen to have a specific range of anesthetic effect where they perform best. Two features quantify the amount of burst suppression that is associated with deep anesthesia. Two other features express the amount of high frequency (beta) activity, reflecting moderate or light sedation. Combining these variables –using a nonlinear algorithm generated by an iterative process of data modeling– produces BIS, which ranges from 100 (awake) to 0 (minimal brain activity) and decreases continuously with increasing hypnosis. BIS was initially correlated with movement to surgical incision and intubation (Kearse, Manberg, Chamoun, deBros & Zaslavsky, 1994; Kearse, Manberg, deBros, Chamoun & Sinai, 1994; Leslie et al., 1996; Mi, Sakai, Takahashi & Matsuki, 1998; Sebel, Bowles, Saini & Chamoun, 1995; Sebel et al., 1997; Vernon, Lang, Sebel & Manberg, 1995). Although BIS predicted movement occasionally better than hemodynamic or other EEG variables, results were not uniformly positive. As movement may reflect spinal rather than cortical activity, however, relatively low correlations with cerebral parameters may be expected

(Rampil, 1998). Therefore, BIS was recently developed in relation to cortical functions and behavioral assessments of sedation and hypnosis (for a description of studies see later).

The clinical utility of BIS monitoring is indicated by several studies in which anesthesia was titrated to BIS 60 to 40, typically referred to as "adequate" or general anesthesia (Johansen & Sebel, 2000). Compared to standard clinical practice monitoring hemodynamic stability, BIS-guided anesthetic administration resulted in lower infusion rates of propofol (Gan et al., 1997) and lower volatile anesthetic usage (Johansen, Sebel & Sigl, 2000) in the absence of additional opioid requirement (Song, Joshi & White, 1997). During BIS-guided maintenance, normal hemodynamic responses (Gan et al., 1997; Struys et al., 1998) and less intraoperative movement (Struys et al., 1998) have been reported. Finally, emergence and recovery from anesthesia may be faster with BIS monitoring (Gan et al., 1997; Johansen, Sebel & Sigl, 2000; Song et al. 1997).

Auditory evoked response

Other monitoring techniques of central anesthetic effect have also been proposed. Upon auditory stimulation, the EEG displays specific responses representing the passage of electrical activity from the cochlea to the auditory cortex. These auditory evoked responses (AER) have been studied extensively and been related to auditory information processing during general anesthesia (see Thornton & Sharpe, 1998, for an overview). The AER waveform contains a series of peaks and troughs of different amplitudes and latencies. Midlatency-auditory evoked potentials (MLAEP) arise 10 to 100 ms after auditory stimulation and appear most suitable for monitoring depth of anesthesia as they show graded changes with anesthetic concentration (Thornton, Konieczko et al., 1989). In contrast, brain stem responses (0 to 10 ms) tend to be unaffected by anesthetics (Schwender, Madler, Klasing, Peter & Pöppel, 1994; Thornton, Konieczko et al., 1989) whereas the late cortical responses (100 to 1000 ms) are heavily attenuated (Plourde, Joffe, Villemure & Trahan, 1993; Van Hooff et al., 1995). Importantly, neuromuscular blocking drugs do not affect the AER (Thornton & Jones, 1993). The MLAEP is a transient response elicited by stimulation rates near 10 clicks per second (10 Hz). When a train of stimuli is delivered at a sufficiently fast rate, responses to successive stimuli overlap and a steady state response occurs. This *auditory steady state response* (ASSR) reaches an amplitude maximum at stimulation rates near 40 Hz (Plourde, 1993). Furthermore, at certain stimulation frequencies, power may be observed at a particular frequency in the absence of power at other frequencies, referred to as the *coherent frequency*, or CF (Munglani, Andrade, Sapsford, Baddeley & Jones, 1993). The next section discusses MLAEP, ASSR, and CF in relation to information processing during anesthesia.

Whereas the awake MLAEP is characterized by three waves of high amplitude and short latency, anesthesia tends to reduce amplitudes and to lengthen the latency of specific peaks (termed Pa, Pb) and troughs (Na, Nb) (Schwender, Madler et al., 1994; Thornton, Creagh-Barry, Jordan & Newton, 1993). According to Davies and colleagues (Davies, Mantzaridis, Kenny & Fisher, 1996), Pa and Nb latency best discriminated between consciousness and unconsciousness in terms of response to command ("squeeze my hand"). Positive response to command has been associated with Nb latencies of 46 ms or shorter (Newton et al., 1992; Thornton, Barrowcliffe et al., 1989) but sensitivity of Nb latency for detecting responsiveness appears low. When anesthesia is deepened, Nb latency increases (to 54 ms) and response to command is lost (Newton et al., 1992). Short Nb latencies and awake MLAEP patterns have also been associated with conscious recall (Newton et al., 1992; Schwender, Klasing, Madler, Pöppel & Peter, 1993). In order to assess MLAEP characteristics for implicit memory, Schwender and colleagues played cardiac surgical patients an audiotape with the story of Robinson Crusoe following sternotomy (Schwender, Kaiser, Klasing, Peter & Pöppel, 1994), and recorded MLAEP shortly before and after audiotape presentation. In patients with implicit memory, demonstrated by free association to the cue "Friday" with responses related to the Crusoe story, Na and Pa latencies resembled an awake MLAEP (20 and 36 ms, respectively). In contrast, prolonged latencies (near 55 and 80 ms, respectively) were observed in patients who displayed no implicit memory for the Crusoe story. In a similar vein, Villemure and colleagues observed increased Nb latencies in patients without implicit memory for words presented during abdominal hysterectomy (Villemure, Plourde, Lussier & Normandin, 1993). It is difficult, however, to separate the effect of small behavioral changes from the profound effect that anesthesia imposes on the AER (Newton et al., 1992).

With respect to the CF and ASSR, Andrade and colleagues (Andrade, Munglani, Jones & Baddeley, 1994; Munglani et al., 1993) administered a series of cognitive tests in volunteers breathing various concentrations of isoflurane. With increasing concentration, CF decreased as well as psychological performance, and three levels were discriminated: conscious awareness with explicit memory (CF = 32.8 Hz), without explicit memory (CF = 24.8 Hz), and absence of responding with no implicit memory (CF = 14.8 Hz). In a different study, these investigators observed a 0.47 correlation between CF and short-term memory performance during propofol sedation (Andrade, Sapsford, Jeevaratnum, Pickworth & Jones, 1996). Apparently, variation in immediate information processing is only partially captured by CF (i.e., $R^2 = 0.22$). With increasing isoflurane concentration (0.26% to 0.5%), the ASSR amplitude has been reported to decrease from 0.24 µV to 0.04 µV (Plourde, Villemure, Fiset, Bonhomme & Backman, 1998). Responsiveness also declined and a 0.95

prediction probability for loss of consciousness has been reported for the ASSR (Plourde & Picton, 1990; Plourde et al., 1998).

Isolated forearm technique

The IFT, mentioned earlier to illustrate the imperfect relation between intraoperative awareness and postoperative conscious recall, has been used in a considerable number of studies but rarely simultaneously with auditory presentation of specific information during anesthesia. Using the IFT and a ten-word stimulus list, Millar and Watkinson (1983) observed response to command in 33% of patients undergoing gynecological surgery and significant detection of target stimuli on a postoperative recognition task, in the absence of conscious recall. King et al. (1993), in contrast, observed patient response rates of 33% (intubation) and 97% (incision), but no cued recall of words played during these periods. In a study by Russell and Wang (1997), no patient responded to command during surgery and no evidence of intraoperative word priming was thereafter found. In a more recent study, response to command was observed but evidence of explicit or implicit memory was again not found (Russell & Wang, 2001). A problematic feature of the latter two studies is that patients were premedicated with a benzodiazepine (temazepam), which typically causes anterograde amnesia. Patients could thus have processed the information, as they processed and responded to the commands, but a trace would be hard to find in such instances. While these studies suggest that IFT monitoring may prevent information processing and memory function during anesthesia, observations are limited. Also, response to command may be hard to distinguish unequivocally from spontaneous movement. The use of IFT as an (online) monitor of anesthesia is further complicated by the fact that the technique itself relies upon the auditory channel. IFT may indicate that information is being processed but it cannot monitor perception of information other than the command, like memory test material. Therefore, the technique is of limited use to memory research during anesthesia. The same applies to AER-related measures that depend upon auditory clicks to be obtained.

BIS, consciousness and recall

Flaishon et al. (1997) examined the ability of BIS to predict return of consciousness as measured by IFT. They administered 40 presurgical patients a single bolus of either thiopental (4mg/kg) or propofol (2 mg/kg) and assessed consciousness by asking patients to squeeze the investigator's fingers once and then twice. No response to command was observed below BIS 59. Consciousness was regained more rapidly at high BIS values than at lower values. When BIS was 65, patients recovering in the propofol bolus group had a less than 5% chance of regaining consciousness within 50 seconds. For thiopental, the probability of awareness was even smaller. Importantly, recorded times until recovery of consciousness varied widely between patients, illustrating the potential for awareness during intubation and skin incision in patients in whom drugs wear off rapidly.

To allow for more subtle assessments of sedation, other investigators have observed response to increasingly intense stimuli. Scores on the Observer Assessment of Alertness/Sedation (OAA/S) scale typically range from 5 (alert) to 0 (deep sleep), depending upon response to one's name (score 5 to 3) and to mild prodding, shaking or noxious stimulation (score 2 to 0). In studies using the OAA/S, consciousness is usually defined as scores of 3 and higher. An overview of findings is displayed in Table 1. High correlations between OAA/S and BIS (r = 0.91) have been reported for sedation with sevoflurane, whereas SEF, MF and end tidal concentrations were found to change less consistently with level of sedation (Katoh et al., 1998). Liu and colleagues (Liu, Singh & White, 1996) administered 4.5 to 20 mg midazolam in increments of 0.5 to 1-mg bolus to patients scheduled for elective surgery until they became unresponsive. BIS related well to OAA/S scores during sedation onset (r = 0.82) and moderately well to responsiveness during recovery (r = 0.60). With increasing sedation, SEF decreased (r = 0.46) as did beta power, whereas alpha power increased. During recovery, none of these variables changed significantly and no consistent changes for the theta or delta power bands, nor for MF were found in this study (Liu, Singh & White, 1996). Good correlations between BIS and OAA/S have been observed during onset (r = 0.74) and recovery (r = 0.71) of propofol sedation as well (Liu, Singh, White, 1997). In this study, SEF did not change significantly during sedation onset. BIS was found to predict consciousness versus loss of consciousness accurately, as expressed by prediction probabilities of 0.94 to 0.99, and more accurately than other EEG parameters or targeted and measured concentration propofol (Glass et al., 1997; Iselin-Chaves et al., 1998; Katoh et al., 1998; Kearse et al., 1998). In these early studies with BIS, early in the sense of the algorithm (version 3.0) used to derive BIS, prediction accuracy was generally good at high BIS values whereas patient variation in responsiveness tended to increase at lower values.

BIS tends to be independent of anesthetic regimen and is reportedly largely insensitive to the differential effect of midazolam, propofol, isoflurane (Glass et al., 1997). With algorithm 3.0 and propofol, 50% of patients lost consciousness in terms of OAA/S responsiveness at BIS values near 65, and 95% of patients at values near 50 (Glass et al., 1997; Iselin-Chaves et al., 1998). Alfentanil supplements may yield quicker loss of consciousness, i.e., at higher BIS values (Iselin-Chaves et al., 1998). Nitrous oxide has a similar effect when administered concurrently with propofol (Kearse et al., 1998), although the agent is a weak sedative by itself (Rampil, Kim, Lenhardt, Negishi & Sessler, 1998).

Table 1. BIS during sedation: Overview of studies using the Observer Assessment of Alertness/Sedation (OAA/S)-scale.

				OAA/S						
Study	Sedative	*N*	Descriptive	5	4	3	2	1	0	*r*
Katoh *et al.* (1998)	sevoflurane	69	Median	95.8	78.3	73.1		66.1	40.1	*0.911*
	(0.2 to 1.8%)									
Liu *et al.* (1996)	midazolam	26	Mean (SD)	95.4	90.3	86.6	75.6	69.2	-	*0.815*
	(4.5 to 20mg)		*during onset*	(2.3)	(4.5)	(4.6)	(9.7)	(13.9)		
			Mean (SD)	-	90.8	82.3	75.2	69.2	-	*0.596*
			during recovery		(6.0)	(7.3)	(10.2)	(13.9)		
Liu *et al.* (1997)	propofol	10	Mean (SD)	94.5	93.3	89.0	80.1	75.6	-	*0.744*
	(220 to 560 mg)		*during onset*	(2.9)	(3.3)	(6.1)	(8.7)	(7.5)		
			Mean (SD)	-	93.8	84.9	82.4	75.6	-	*0.705*
			during recovery		(0.8)	(5.9)	(10.5)	(7.5)		
Iselin-Chaves *et al.*	propofol	40	LOC$_{50}$ (range)				64 (61 - 66)			
(1998)	(0 to 6 µg/ml)		LOC$_{95}$ (range)				49 (45 - 54)			
	+ alfentanil		LOC$_{50}$ (range)				67 (64 - 69)			
	(50 ng/ml)		LOC$_{95}$ (range)				63 (57 - 70)			
	+ alfentanil		LOC$_{50}$ (range)				72 (67 - 76)			
	(100 ng/ml)		LOC$_{95}$ (range)				54 (45 - 64)			
Kearse *et al.* (1998)	propofol	20	LOC$_{50}$ (95%CI)				65.2 (63 - 67.6)		-	
	(0 to 4 µg/ml)		LOC$_{95}$ (95%CI)				53.8 (48.7 - 59)			
	+ N$_2$0 (30%)		LOC$_{50}$ (95%CI)				75.7 (71.2 - 80)		-	
			LOC$_{95}$ (95%CI)				68.3 (60.5 - 76)			

OAA/S-score: 5 = patient responds readily to name spoken in normal tone, 4 = lethargic response to name spoken in normal tone, 3 = responds only after name is called loudly and/or repeatedly, 2 = responds only after mild prodding or shaking, 1 = does not respond to mild prodding or shaking/ responds only after noxious stimulation, 0= does not respond to noxious stimulation. LOC= loss of consciousness, in 50% of patients (LOC$_{50}$) and 95% of patients (LOC$_{95}$).

Reports that certain drug combinations alter BIS readings may reflect the use of algorithms that were more sensitive to differential drug effects.

Before affecting consciousness, anesthetics attenuate conscious recall. Patients may respond to command in the absence of conscious recall for information presented to them while being responsive. Liu et al. (1998) assessed conscious recall for pictures shown at different levels of propofol sedation and observed 100% recall in fully alert participants, corresponding to a BIS value of 95.4 on average. Recall rapidly declined to 63% when responding was lethargic (BIS = 93.4) and further to 40% when response was virtually absent (BIS = 87.3) whereas conscious recall was absent in unresponsive (BIS = 80.8) participants. Iselin-Chaves et al. (1998) reported similar findings, in addition to an increased probability of conscious recall when alfentanil had been given with propofol. This observation does not necessarily reflect an effect of alfentanil on memory. As consciousness may be lost quicker when alfentanil is given, anesthetic concentration is likely decreased, resulting in a higher probability of information processing and memory function. In a different study, Glass et al. (1997) presented volunteers with a picture or word at several concentrations of propofol, midazolam or isoflurane, and subsequently assessed free and cued recall. Although the relation between BIS and recall was statistically comparable for the various anesthetics, the memory curve appeared flatter for isoflurane than for propofol and midazolam, suggesting potentially different relations to memory function. Pooled data in this study showed a 50% probability of recall at BIS values near 86 that declined to 5% at BIS values near 65. As with consciousness, recall was accurately predicted at high BIS values but interpatient variability increased at lower values in these studies. At the same time, the probability of recall may be overestimated due to flawed memory assessment. When correct identification of presented stimuli is taken as evidence of memory, chance performance is included as well.

BIS and implicit memory

An important characteristic of the memory studies discussed so far is that participants were asked to what extent they remembered or recognized material presented previously during anesthesia. The tasks that will be discussed next can be performed without referring to the learning episode, and even when participants are instructed to remember presented material, tasks can be completed without conscious recollection. In that case, participants respond with whatever comes to mind.

Highly important is a recent study by Lubke, Kerssens, Phaf and Sebel (1999), who investigated memory function in 96 patients with minor and severe physical trauma, thereby including a wide variety of hypnotic states. After induction with etomidate, patients were played 16 target words via headphones. Each word was presented consecutively for 3 min and time locked to several indicators of hypnotic state, including BIS. This allowed hypnotic state during word presentation to be related to postoperative memory performance. BIS (± SD) during word presentation was on average 54 ± 14 (range 20 to 97). Six hours to six days after surgery, with an average of 42 hours postoperatively, patients performed a word stem completion task in which they were instructed to use word stems (e.g., FAN) as a cue to recall intraoperatively presented words (e.g., fancy). In case recall failed, the first word coming to mind was to be used for stem completion. In addition, the PDP was used and patients were instructed to use presented words in one part of the test (inclusion condition), and to avoid such words in the other part (exclusion condition) by using a different word for stem completion (e.g., fantastic). A word like -fancy- could be named by sheer chance, a probability reflected by the frequency with which it occurred for stem completion without prior presentation during anesthesia (distractor hit rate, also referred to as base rate). Memory would be evident when words presented during anesthesia were used more often than base rate, and this was exactly what we observed in the inclusion part of the word stem completion test: patients were more prone ($p < 0.001$) to say "fancy" when it had been presented during surgery than when it had not (Lubke et al., 1999). Because both conscious and unconscious influences of memory lead to responding with target words in this part of the test, the exclusion part could indicate whether patients exerted control over their responses by avoiding target words, reflecting a more conscious level of word processing.

No sign of response control was observed in the trauma study, however, providing strong evidence for an unconsciously mediated memory effect. Furthermore, a model in which the probability of memory varied across patients provided a better data fit than a model in which the probability was equal for all patients (Lubke et al., 1999). Because depth of anesthesia was the only relevant factor that varied considerably in this group of patients, variation in memory was explained in terms of individual differences in hypnotic state. Observed hit rates supported this notion and clearly declined with deepening hypnosis, as reflected by categorized BIS-levels, suggesting dependency of memory function upon hypnotic state as well. Moreover, patients still displayed memory for words presented at BIS levels assumed to indicate adequate anesthesia, i.e., at BIS between 40 and 60. Finally, of the various parameters that were monitored (SEF, MF, mean arterial pressure, heart rate and end-tidal isoflurane concentrations), only BIS predicted memory performance, albeit weakly ($R^2 = 0.12$). Thus, the utility of BIS as an instrument for signaling implicit memory function seems limited.

Struys et al. (1998) found no evidence of memory function during adequate hypnotic state monitored by BIS in 58 female patients undergoing gynecological surgery with propofol anesthesia. They played patients a 15-min audio tape containing the story of Robinson Crusoe while targeting BIS to remain between 40 and 60 in one (experimental, n

= 28) group whereas classical signs of hypnotic adequacy guided anesthesia in the other (control, n = 30) group. Average BIS readings throughout the surgical procedure did not differ for the two groups and none of the patients reported conscious recall after recovery. Implicit memory for the Crusoe story was reported to occur less often in the BIS guided anesthetics (n = 0) than in the standard monitoring group (n = 3), although the investigators failed to establish base rate performance (3 out of 30 people may associate Friday to Robinson Crusoe without prior presentation of the story). Despite this fallacy in study design, the results obtained by Struys et al. (1998) contradict those of Lubke et al. (1999) and instead suggest absence of memory function when BIS drops below 60.

Preserved memory function, however, may depend on the type of patient and surgery. Vigilance and information processing appears more vital to a trauma patient who fears for his or her life than for a patient undergoing elective surgery. Hence, the former may display signs of information processing and memory function, as Lubke et al. (1999) observed, whereas the latter, studied by Struys et al. (1998), may not. Circumstantial variables like psychological and physiological stress, the emotionality of the surgical setting and the relevance of information to one's survival and well-being, could make a difference when it comes to cognitive functioning during anesthesia.

Lubke, Kerssens, Gershon and Sebel (2000) continued to investigate memory function during a surgical procedure where the hypnotic state is known to be light. They played 24 female patients having undergone emergency cesarean section, a set of words while patients breathed 70% N_2O in oxygen supplemented with 0.2% isoflurane and morphine. The memory paradigm and stimuli were adopted from the trauma study (Lubke et al, 1999), but this time, BIS during word presentation was considerably higher and averaged (± SD) 76.3 ± 3. None of the patients consciously recalled any intraoperative events or words, but in contrast to the trauma study, patients made correct inclusion–exclusion decisions, indicating they controlled their responses without conscious awareness. An estimation procedure revealed a significant probability of explicit memory function and this exceptional finding was thus referred to as unconscious–controlled memory (Lubke et al, 2000).

In summary

Explicit memory after general anesthesia is a rare phenomenon whereas implicit memory for specific information presented intraoperatively has been observed reliably. Because implicit memory does not guarantee unconscious information processing, controversy remains over whether or not patients process information outside conscious awareness, during so-called *adequate* anesthesia. With the use of PDP and EEG bispectral index, a novel parameter of hypnotic adequacy, preserved memory function has been demonstrated in one study with trauma patients. In patients undergoing elective surgery, no such evidence has been established so far.

The overview of research hitherto presented addressed investigations into direct and indirect priming effects of stimuli that generally lack emotional meaning or salience. Such stimuli are vital to sound studies of human cognition under anesthesia but bear little on real-life surgical theater where hazardous situations arise and threatening information may be communicated. A clinically relevant question therefore is whether information is processed differently when emotions are involved.

Part II : Emotion

Do we run from a bear because we are afraid or are we afraid because we run?
William James (1884)

The nature of emotion

A major goal of emotion research is to elucidate the relation between arousing stimuli and the conscious feelings we experience. If one considers this relation as a sequence of events (James, 1884), the question is what comes in between. William James, one of the first emotion theorists, noted that emotions are often accompanied by bodily responses, such as a racing heart, tense muscles, and sweaty palms. These physiological responses return to the brain in the form of internal sensations. According to James, such responses and sensations make emotions feel different from other states of mind, and make different emotions feel different. It was the unique pattern of sensory feedback that gave each emotion its unique quality (LeDoux, 1998, chap. 3). James thus proposed that physiological response and sensory feedback were involved in emotion.

Walter Cannon, a physiologist who had been studying bodily response in states of intense emotion, called James' feedback theory into question in the 1920s. He argued that the autonomic nervous system, in particular the sympatic part that was held responsible for the characteristic physiological signs of emotional arousal, acted uniformly regardless of how it was activated and could not account for why different emotions felt differently. Furthermore, Cannon noted that the sympatic response system was far too slow to account for feelings. He recognized that bodily feedback was important to emotion but it could not account for differences between emotions. The debate over emotion subsided for a substantial period of time under the influence of Behaviorism with its emphasis on observable, objective behaviors. Mental and physiological states were dismissed as research objects and came to be known as "ghosts in the machine". Around 1950, the New Look movement challenged the behaviorist notion by arguing that internal factors were to be taken into account, and by showing that subjects could have autonomic nervous system responses to emotional stimuli in the absence of conscious awareness of the stimuli (Lazarus & McCleary, 1951).

The debate on the nature of emotions revived in the 1960s with Schacter and Singer (1962), who demonstrated that we tend to label bodily arousal based on information about the physical and social context we find ourselves in, and knowledge about situation-appropriate emotions. In explaining the gap between nonspecific bodily arousal and specific feelings, Schacter and Singer proposed that cognitive interpretations (attributions) accounted for the specificity of felt emotion. The notion of attribution did explain how emotional responses were dealt with once they occurred, but not what generated the response in the first place (LeDoux, 1998, chap. 3). In addressing this question, Arnold conceived of an appraisal mechanism in the brain that evaluated the significance of stimuli in terms of potential harm or benefit. Appraisal supposedly led to an action tendency toward or away from anything assessed as good or bad, and according to Arnold, it was the felt tendency that accounted for emotion and conscious feelings. Because different appraisals elicit different action tendencies, we distinguish various emotions. In contrast to James, Arnold only required an action tendency rather than actual behavior for feelings to occur.

Lazarus adopted the appraisal concept, amongst others, and demonstrated that interpretations of situations strongly influenced the emotions experienced. He proclaimed primacy of cognition (Lazarus, 1984) and considered it to be both a necessary and a sufficient condition of emotion (Lazarus, 1991). Like Arnold, Lazarus recognized that appraisals could be unconscious and that emotions could be initiated automatically, yet he emphasized the role of consciousness and higher thought processes in emotion. Treating affect as postcognitive and describing it as a state occurring only after considerable mental operations had been accomplished, cognitive appraisal theories diminished the distinction between emotion and cognition. Theorists heavily relied on self-report measures by assuming we have introspective (i.e., conscious) access to the unconscious processes giving rise to emotion. This assumption is questionable, however, as is the validity of data obtained (e.g., Nisbett & Wilson, 1977). In 1980, Robert Zajonc challenged the cognitive account of emotion and postulated affective primacy over cognition (Zajonc, 1980). His renowned article titled "Feeling and Thinking: Preferences Need No Inferences", revived an old notion: the emotional unconscious.

Affective primacy

Zajonc (1980) stated that affective reactions could occur without extensive perceptual and cognitive encoding, were made with greater confidence than cognitive judgments, and could be made sooner. The fact that cognitions produced feelings, he said, did not imply that cognitions were a necessary component of affect. Zajonc listed a number of arguments why thoughts and feelings should be distinguished, and reviewed empirical evidence supporting affective primacy. Foremost, his argument evolved around the *mere exposure effect*, the phenomenon that preference for objects can be induced by virtue of mere (i.e., unreinforced) repeated exposure. He himself had bumped into the phenomenon when he noted a relation between word frequency count –the number of times a word appears in various written sources– and the evaluative meaning of a word, as well as between word frequency and attitudes toward the object described by a word (Zajonc, 1968). In a series of experiments with nonsense words, Chinese ideographs, and photographs of faces, Zajonc (1968) demonstrated a positive relation between frequency of exposure and the extent to which stimuli were rated to connote "good" versus "bad" affect on a seven-point scale. Exposure frequency also related negatively to changes in galvanic skin response, suggesting that repeated exposure induced habituation and decreased autonomic arousal when the stimulus was again encountered.

Affective primacy was further supported by structural equation modeling of mere exposure data, indicating a strong link between stimulus exposure and subjective affect, independent of recognition (Zajonc, 1980). Even firmer evidence of the "hot" repeated exposure effect provided two studies in which stimulus recognition had been reduced to chance level (Kunst-Wilson & Zajonc, 1980; Wilson, 1979). Liking of visual and auditory stimuli still varied with the objective history of stimulus exposure. Zajonc (1980) continued to illustrate how information processing was intertwined with affect, using studies of state dependent recall, mood and context effects to his aid, and concluded his monograph by postulating two different forms of unconscious processes: one where behavior was entirely under the influence of affective factors and another that was implicated in highly overlearned, automated information processing which included cognitive acts. A biological basis for a distinct affective system was speculated on, but the available data and techniques could not yet prove its existence nor location. It remained unclear whether it was just a matter of separate storage of affective stimulus features (preferanda) or whether such features were already distinctly registered at encoding.

A large number of controlled studies followed Zajonc's initial demonstrations of the exposure-affect relationship in 1968. In a typical experiment, subjects are presented with varying numbers of exposures to stimuli and a dependent measure of affect is collected for each stimulus using some form of bipolar rating scale. Making up the balance after two decades of research, Bornstein (1989) conducted a meta-analysis in order to assess systematically the influence of critical variables on the size of the exposure effect. He included over 200 independent experiments with unreinforced exposure to visual and auditory stimuli in human subjects, and found an overall combined effect size (r) of 0.26.

This is generally considered a moderately strong effect, and the fail-safe *N* (33,047) and combined z (20.80) indicated that the exposure–affect relationship is robust and reliable.

Bornstein (1989) categorized experiments according to eight methodological variables and analyzed the size of the exposure effect as a function of each. He obtained a significant positive relationship between exposure frequency and reported affect for nearly all types of stimuli, except abstract paintings, drawings and matrices. The effect was strongest with meaningful words (0.49) and moderate for auditory stimuli and nonsense words (0.24). Complex stimuli produced more positive affect than simple stimuli, and for presentation variables, Bornstein observed a decline in the size of the exposure effect as the maximum number of exposures increased. All numbers of presentation (1 to 100+) produced significant changes, but stimuli presented only once to nine times yielded most effect (0.21). In addition, heterogeneous stimulus sequences appeared more effective than homogeneous (massed) presentations, and a considerable effect (0.41) was demonstrated for short exposure durations (< 1 s). This supported Zajonc's claim that conscious awareness was not required for the mere exposure effect to occur. In fact, the combined effect size of sixteen studies using stimuli not recognized at better-than-chance accuracy, was much larger (0.53) than the mean effect size for all experiments. Bornstein concluded that stimulus recognition could actually inhibit the exposure effect. Finally, various types of measures produced the effect, which was generally larger after delayed testing as opposed to immediate rating of stimuli.

Affective priming

While the mere exposure paradigm provided incontrovertible evidence that affective reactions could take place in the absence of conscious awareness of stimuli, it did not prove that affective qualities were processed more readily than their nonaffective attributes, as the affective primacy hypothesis (Zajonc, 1980) asserted. Clearly, more direct evidence was needed. Zajonc and colleagues therefore conducted a series of experiments comparing the influence of affective and nonaffective stimulus features under degraded (i.e, suboptimal) and good (optimal) viewing conditions (Murphy & Zajonc, 1993). In the optimal condition, stimuli were shown for 1 s which allowed subjects to clearly see them. In the suboptimal condition, stimuli were shown for 4 ms only. In both conditions, stimuli were immediately followed by a second stimulus, a Chinese ideograph (or character), which subjects rated on various dimensions across different studies. The ideographs represented a novel, neutral stimulus suitable for measuring changes in subjects' perceptions due to the previous presentation of the first stimulus, the prime. Murphy and Zajonc (1993) used primes with either strong affective content (pictures of male and female faces expressing happiness and anger) or emotionally bland content (large and small, symmetrical and unsymmetrical shapes). The use of the former designated affective priming and that of the latter cognitive priming. The two forms of priming and thus information processing were compared across studies. If affective reactions were more immediate and less under voluntary control, as the affective primacy hypothesis suggests, affective stimuli presented outside of conscious awareness were expected to influence judgments to a larger extent than non-emotional stimuli. Hence, affective priming would have to be superior to cognitive priming under such conditions.

Murphy and Zajonc (1993) conducted five experiments. In each, a forced-choice test of awareness assured that primes in the suboptimal viewing condition were not recognized above chance level. In the first two studies, affective primes were used and subjects rated, on a 5-point Likert scale, to what extent they liked the Chinese ideographs (Study 1) or to what extent it represented a "good" or "bad" object (Study 2). In both studies, suboptimal affective primes produced a significant shift in subjects' ratings of the ideographs. Positive primes yielded higher liking (*M* = 3.46) and goodness ratings (*M* = 3.28) than negative primes (*Ms* = 2.70 and 2.61, respectively), and both differed significantly from a control condition in which no prime or an irrelevant prime preceded the ideographs (mean rating just above 3.0 in both studies). The same primes presented under optimal viewing conditions, however, produced no effect at all. Thus, the magnitude of the affective priming effect related inversely to the length of exposure to the primes, with only suboptimal exposures having an effect. Priming with nonaffective stimuli, investigated in three subsequent studies, yielded the reverse pattern of results and showed effects primarily under lengthily exposure durations. Stimuli varying on dimensions such as size (Study 3), symmetry (Study 4) and gender (Study 5) influenced judgments of the ideograph's size, symmetry and gender representation only in the optimal priming conditions. These findings were consistent with the notion that affective priming is superior to cognitive priming under suboptimal stimulus exposures, and thus confirmed the affective primacy hypothesis.

In their quest to demonstrate that affect is not a mere cognition, Zajonc and colleagues continued to explore qualitative differences between conscious and unconscious affect using their priming paradigm with optimal and suboptimal stimulus exposures. In subsequent research, they focused on the diffuse, undedicated nature of unconscious affect (Murphy, Monahan & Zajonc, 1995). It could disperse, fuse, blend, combine and become attached to totally unrelated stimuli in suboptimal viewing conditions, which cognitive priming apparently could not. To test the hypothesis that unconscious affect is diffuse, whereas affect whose source we are consciously aware of is not, the investigators induced affect from two sources (repeated exposure and affective priming) and examined the way in which the two effects combined. Because the source of affect typically remains unavailable in the mere exposure paradigm regardless of exposure duration, a mere exposure effect was expected under both optimal and suboptimal viewing conditions. Based on the aforementioned studies, affective priming was expected to modulate feelings in the suboptimal condition only. In a sophisticated series of experiments, participants were exposed once or three times to Chinese ideographs at 4-ms suboptimal (Studies 1 and 3) or 1,000-ms optimal (Studies 2 and 4) viewing conditions, after which affective priming of ideographs was induced suboptimally (Studies 1 and 2) or optimally (Studies 3 and 4) using the same facial stimuli as before (Murphy & Zajonc, 1993). In this way, the combined effect of priming and exposure at the two exposure durations was examined. In each study subjects made two judgments about presented and not presented ideographs: how much they liked it on a 5-point scale and whether or not they thought it had been shown before. Finally, a forced-choice test of awareness for the primes was administered.

In all four studies, recognition of suboptimally presented primes and ideographs never exceeded chance accuracy (Murphy, Monahan & Zajonc, 1995). Overall, liking ratings became more positive as frequency of exposure increased from zero (M = 2.78) to one (M = 2.97) to three (M = 3.34) exposures. No interactions with stimulus duration were found, demonstrating that the exposure effect was indeed operant under both optimal and suboptimal viewing conditions. Liking ratings also became more positive as the valence of primes changed from negative to positive, but here, the effect interacted with exposure duration. Ratings were significantly more positive (M = 3.35) and negative (M = 2.65) when facial primes had been presented suboptimally as compared to optimal presentations (M = 3.01 versus M = 3.07), indicating that affective priming was more effective in the suboptimal condition. Furthermore, suboptimal positive priming (Studies 1 and 2) added a constant to the affect generated by exposure frequency whereas negative priming subtracted a constant in such conditions. Thus, when subjects were unaware of primes being presented, affect combined in a roughly additive fashion with repeated exposure effects. When affective primes were presented at optimal durations and open to conscious awareness, the effect disappeared. According to Murphy, Monahan and Zajonc, this qualitative difference highlighted one property of unconscious affect, namely that "it is relatively diffuse and can become attached to unrelated stimuli".

In summary

Although consciousness and cognition may influence the way we feel, awareness and stimulus recognition are not necessarily required for simple emotional reactions to stimuli, such as preferences. Two sources of unconscious affect may be distinguished, one resulting from mere (unreinforced) repeated exposure to stimuli, and one that can be induced by (reinforced) exposure to positive and negative stimuli whose affective qualities are diffuse and become attached to unrelated, emotionally bland stimuli. Whereas the former is a naturally occurring emotional response to a wide range of stimuli, the latter implies processing of emotional stimulus attributes in particular. Outside conscious awareness, the two sources of affect may combine in a roughly additive fashion.

The emotional brain[1]

Returning to the question what comes in between arousing stimuli and the conscious feelings that we experience, psychologists have mainly been concerned with the efferent (output) side of the stimulus-to-feeling sequence. It suits their nature to observe human behavior in general and emotional behavior in particular. As a science, psychology is rather inductive in the logical sense of the word. The mechanisms underlying behavior are inferred from external phenomena and observations. Modern brain science, on the other hand, focuses on the afferent (input) side of behavior and aims to figure out where functions are located in the brain. Both sciences have their merits and shortcomings, and fortunately, a mutual interest and synthesis of data is not uncommon. Because I have not attempted to study emotion in a neurophysiological sense, this section highlights a few notions relevant to the argument of the investigation.

Functional localization is an old and well-accepted notion that mainly has been studied with brain stimulation and ablation techniques (LeDoux, 1998, chap. 4). The former involves passing small electric currents through electrodes inserted in the brain, which artificially reproduces the effects of natural information flow in the brain. Ablation studies reveal brain function through loss of capabilities after (inflicted) brain damage. Using these techniques, scientists pursued the brain's emotional system (see LeDoux, 1998, chap. 4, for a review). According to LeDoux, attempts to find a single unified brain system of emotion have not been not very successful, despite the introduction of a "limbic-system" in the early 1950s, which comprised the amygdala, septum and prefrontal cortex. Albeit influential, the limbic system theory is unacceptable for various reasons, LeDoux recently noted. Instead, he proposed, it is more likely that such a system does not exist and that different networks in the brain mediate different emotions (LeDoux, 1998, chap. 5).

In pursuing one such network, the fear system, LeDoux has used a simple but very effective learning paradigm in his studies with rats. He adopted a variation on the procedure known as classical conditioning, in which an association is created by pairing two stimuli, one that is a natural trigger of a specific –in this case fear– response (the unconditioned stimulus, say a mild yet unpleasant electric shock) and one that becomes the learned trigger (the conditioned stimulus, say a sound). After a few pairings of the sound and the shock, the sound by itself elicits the response pattern formerly associated with the shock. Such *conditioned fear learning* occurs quickly in both animals and humans, is very long

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[1] After LeDoux (1998)

lasting, and does not require conscious awareness of the conditioned stimulus or the association with the unconditioned stimulus. Once a stimulus has been established as a learned trigger of fear, it elicits a host of prototypical physiological and behavioral fear responses each time it occurs. In this way, fear conditioning provides for a controlled yet powerful experimental technique to study the brain's fear mechanism.

Using ablation, fear conditioning and neuronal staining techniques, LeDoux (1998, chap. 6) traced the fear pathway to the amygdala, a subcortical region below the auditory thalamus. He also discovered a highway and a by-way from the auditory thalamus to the amygdala, one that involved the cortex (cortico-amygdaloid pathway) and one that surpassed it (thalamo-amygdaloid pathway). Both served different functions as well. The cortical pathway is "narrowly tuned" and responds to specific cues only. This allows making fine distinctions between what is responded to and what is not, serving situation-appropriate responding. Although cortical damage need not necessarily affect emotional responses, removal of the cerebral cortex in animals is associated with deregulation of emotional response. In such decorticate animals, emotional reactions are easily provoked (see Damasio, 1994, for case studies of prefrontal lobe damage in humans). The direct pathway to the amygdala, in contrast, responds to a much wider range of stimuli and leaves little room for maneuver. This pathway, however, is twice as fast as the cortical route and thus serves an important advantage in time (it only takes about 12 ms for an auditory stimulus to reach the amygdala directly via the thalamus). The human amygdala is also able to discriminate between stimuli on the basis of their acquired (conditioned) significance and brain neuroimaging has indicated that this response is lateralized according to the level of stimulus awareness (Morris, Öhman & Dolan, 1998).

Specific, subcortical regions of the brain thus mediate swift processing of emotionally relevant and potentially harmful information. The amygdala fits the appraisal mechanism that cognitive emotion theorists such as Arnold had in mind, and seems to confirm Zajonc' (1980) hunch that affective stimulus features are registered very early and distinctively in the information processing flow. Given that appraisal of emotional meaning is a basic biological function rooted in subcortical areas of the brain, emotional reactions and information may be expected during general anesthesia as well.

Emotion during anesthesia

Ghoneim, Block and Fowles (1992) studied classical conditioning of skin conductance responses in 31 female patients who received 1 MAC isoflurane in nitrous oxide for minor gynecological surgery. The unconditioned stimulus was a loud noise that was paired with a specific target word in the conditioning phase during anesthesia. Although conditioned skin conductance responses could be elicited in a control group consisting of 26 volunteers who received no anesthesia, there was no evidence of conditioning in any of the patients. With lower concentrations (0.12 to 0.50 MAC) of isoflurane, Dutton and colleagues (Dutton et al., 2002) just recently observed dose dependent suppression of fear conditioning in rats using freezing to tone as an outcome measure. At maximum concentration, rats showed minimal freezing.

Mere exposure

Few have looked into stimulus preference after mere repeated exposure during anesthesia. Block, Ghoneim, Sum Ping and Ali (1991) played a series of sixteen 5-letter nonsense words either twice, four, eight or 16 times to 72 women undergoing gynecological surgery. Postoperatively, patients heard pairs of words consisting of one nonsense word that had been played during anesthesia and one that had not. They had to guess which had been played to them, and in a separate session (the order of which was counterbalanced), and to decide which word sounded more pleasant. Patients both preferred and recognized more accurately the nonsense words that had been played to them most frequently relative to those played less frequently. Hence, the investigators demonstrated a mere exposure effect. In this study, hypnotic state was not controlled for. Half of the patients received isoflurane and 70% N_2O in oxygen to produce 1.3 MAC, the other half received 70% N_2O in oxygen with opioids (fentanyl or alfentanil). With a similar group of patients, anesthetic and two-alternative forced-choice task, Rondi et al. (1993) found no effect for twelve 10-s Japanese melodies that had been played 8 times during anesthesia. Winograd, Sebel, Goldman and Clifton (1990) did observe increased preference for ten 30-s traditional ethnic music selections played three times compared to melodies which had not been presented, but only in unanesthetized control subjects. The effect disappeared when the melodies were played during anesthesia (maintained with N_2O/O_2/isoflurance and fentanyl). If one keeps the effect of delayed testing in mind (Merikle & Daneman, 1996), one explanation for these null results may be found in testing of patients after more than 36 h. Block et al. (1991), in contrast, tested their patients on the day after surgery.

Positive suggestions

Egbert, Battit, Welch and Bartlett (1964) reported that patients briefed about their operation before surgery subsequently had lower analgesic requirements and shorter postoperative stays in hospital than control patients to whom minimal information had been given. This suggested that psychological interventions could help speed up recovery from surgery and a number of researchers aimed to influence patients for the better by presenting therapeutic suggestions during their operation (see Andrade, 1995, for a review). Results were mixed and methodologies often flawed, however (Andrade, 1995). Patients were typically given various suggestions and evaluated on various indices of recovery. It is also unclear what mediates therapeutic effect. To establish the merits of these studies, Merikle and Daneman (1996) analyzed 14 studies involving 1092 patients who had been presented positive suggestions during anesthesia. The small and insignificant overall effect size (0.06) indicated poor evidence of beneficial effect on duration of hospitalization. Four other studies, however, in which patients (n = 234) had postoperatively been given the opportunity to administer their own painkillers using patient controlled analgesia devices (PCA), indicated some evidence that the suggestions influenced the pain experienced following surgery.

The lack of evidence for emotional information processing during general anesthesia contrasts sharply with the abundant evidence for such processing outside conscious awareness observed in behavioral and neurophysiological studies of emotion in humans and animals in the laboratory. These studies suggest that emotional reactions may be well preserved during anesthesia and are more likely to occur than non-emotional manifestations of information processing. One explanation for the controversy may be found in the limited level of processing of stimuli rendered unconscious to phenomenal awareness (Greenwald, 1992). Instead of using simple affect manipulations, however, studies during anesthesia have relied on sentences conveying emotional information, which seem far too complex to be processed when attention and consciousness are severely attenuated. In addition, a wide range of variables other than intraoperatively induced emotion may affect the outcome measures that have generally been used in suggestion studies. A more objective and relevant measure, by contrast, could provide stronger evidence of emotional information processing, as the few studies with patient controlled analgesia suggest. When used in combination with simple affective stimuli, emotional responses during anesthesia may be demonstrated after all.

Synopsis

This thesis addressed two prevailing issues over memory function during anesthesia (i.e., do patients process information outside conscious awareness, and is emotional information being processed?) in four experiments that will be presented in the chapters to follow. Two studies investigated memory function during adequate hypnosis (general anesthesia) as monitored by EEG bispectral index (BIS 40 to 60), and two during deep sedation (BIS 60 to 70). In the first study (chapter 2), patients under general anesthesia were played category exemplars for which a memory effect had previously been found without controlling for hypnotic state, however. In the second study (chapter 3), we played patients a series of relatively familiar Dutch words during deep sedation, and postoperatively tested their memory with a word stem completion task. In this study, we also assessed response to command using the isolated forearm technique, and were surprised to find considerable responsiveness as well as conscious recall. A posthoc exploration of these phenomena is described in chapter 4. To address the influence of emotional information on memory function, a third and fourth study played patients during anesthesia with a simple yet potent emotional stimulus (a positive sound) prior to half of the words (affective priming condition), while the other half was just repeatedly presented (mere exposure condition). Both studies used the same word series and memory test as were employed in the second study, and also included a set of nonsense words. Patients were presented with the word and sound stimuli during general anesthesia (chapter 5) or deep sedation (chapter 6).

2

Auditory information processing during adequate propofol anesthesia monitored by electroencephalogram bispectral index

Kerssens, Klein, van der Woerd, Bonke (2001)

Abstract

Memory for intraoperative events may arise from inadequate anesthesia when the hypnotic state is not continuously monitored. Electroencephalogram bispectral index (BIS) enables monitoring of the hypnotic state and titration of anesthesia to an adequate level (BIS 40 to 60). At this level, preserved memory function has been observed in trauma patients. We investigated memory formation in elective surgical outpatients during target controlled anesthesia with propofol and alfentanil. While BIS remained between 40 and 60, patients listened to a tape with either familiar instances (exemplars) from two categories (experimental [E] group, n = 41) or bird sounds (control [C] group, n = 41). After recovery, memory was tested with direct and indirect measures. BIS during audio presentation was on average (± SD) 44 ± 4.6 and 46 ± 4.8 for groups E and C, respectively. No patient consciously recalled the intraoperative period, nor were presented words recognized reliably (E: 0.9 ± 0.8 hits; C: 0.8 ± 0.8 hits) (p = 0.7). When asked to generate category exemplars, group E named 2.10 ± 1.0 hits versus 1.98 ± 1.0 in group C (p = 0.9). We found no explicit or implicit memory for familiar words presented during adequate propofol anesthesia, at BIS levels between 40 and 60, in elective surgical patients.

Introduction

Various studies have demonstrated implicit (unconscious) memory effects for auditory stimuli presented during general anesthesia (Andrade, 1995; Ghoneim & Block, 1992, 1997; Merikle & Daneman 1996). Such information processing, however, may result from temporary lightening of anesthesia whenever depth of anesthesia is not continuously monitored during stimulus presentation. Also, most of the commonly used memory tests do not differentiate between conscious and unconscious contributions to memory performance (Jacoby 1991; Jacoby, Toth & Yonelinas, 1993). Therefore, it remains unclear to what extent auditory information is processed during general anesthesia. This is not only important with respect to the increasing number of patients claiming recall under anesthesia, but particularly so for the emotional well being of surgical patients (Domino, Posner, Caplan & Cheney, 1999; Osterman & van der Kolk, 1998).

Electroencephalographic (EEG) bispectral index (BIS) is an on-line measure of hypnotic state and a reportedly valuable predictor of consciousness and recall with various anesthetic regimens (Glass et al., 1997; Iselin-Chaves et al., 1998; Katoh, Suzuki & Ikeda, 1998; Kearse et al., 1998; Liu, Singh & White, 1996, 1997; Rampil, 1998; Sigl & Chamoun, 1994). BIS ranges from 100 (awake) to 0 (isoelectric brain). Values between 40 to 60 indicate adequate general anesthesia, reflected by absence of response to command, alertness and recall. Furthermore, titration of anesthesia to BIS 40-60 appears clinically useful in terms of anesthetic requirement and recovery (Gan et al., 1997; Song et al., 1997; Struys et al., 1998). Recently, BIS was related to memory function in trauma patients (Lubke, Kerssens, Phaf & Sebel, 1999). Reliable evidence for implicit memory indicated that information was partially processed, even at BIS levels between 40 and 60. In elective surgical patients, no memory was reported for an auditory story presented at these levels (Struys et al., 1998), but memory assessment was flawed because base rate performance was not established.

In order to investigate information processing during adequate anesthesia for elective surgical procedures, we exposed surgical outpatients to auditory stimuli while BIS remained between 40 and 60. Given our hypothesis that information processing is preserved during controlled adequate anesthesia, we expected implicit memory effects in the absence of conscious recall. We used the same test that reliably demonstrated implicit memory in two previous studies, in which hypnotic state had not been monitored (Jelicic, Bonke, Wolters & Phaf, 1992; Roorda-Hrdlicková, Wolters, Bonke & Phaf, 1990).

Methods

After study approval by the local institutional human investigation committee, written informed consent was obtained from 102 elective surgical outpatients (ASA I-II) at the University Hospital Rotterdam, the Netherlands. Patients were between 18 and 65 years of age, fluent in Dutch, and reported not to suffer from hearing impairment, alcohol or drug abuse or psychiatric illness. Eighteen patients were excluded from data analyses because stimulus processing during anesthesia was theoretically unlikely due to deep anesthesia (BIS below 40 during all word presentations, n = 9; mean BIS + 1 SD below 40, resulting in approximately 85% of presentations below 40 assuming normal distribution, n = 9). In this group of patients there was not enough time for BIS to increase once anesthesia had been induced to a deep level (BIS < 40). One patient was excluded because stimulus processing was theoretically likely due to inadvertent lightening of anesthesia (BIS above 60 during at least 10% of word presentations), and another one due to the use of psychoactive medication. The remaining 82 patients comprised the experimental (n = 41) and control (n = 41) groups.

EEG monitoring and anesthesia

Electrical brain activity was measured by an A1000 monitor (Aspect Medical Systems, Newton, MA) using a two-channel referential montage and four self-prepping electrodes (Aspect Medical Systems, Newton, MA) attached above the left and right outer malar bone (At1 and At2), high on the forehead (Fpz, reference) and approximately 2 cm to the right of the reference electrode (Fp2, ground). Electrode impedance was below 5 kΩ. Recordings of BIS (version 3.2) started before induction of anesthesia and continued till anesthetic emergence.

Patients arrived in the operating room unpremedicated, where they received intravenous anesthesia with propofol. Target-controlled anesthesia was accomplished by using an infusion pump (Ivac, Alaris Medical Systems, San Diego, CA) incorporating a pharmacokinetic model (Diprifusor, Zeneca) targeting plasma concentrations propofol. Target concentration was set at 6 µg/ml for induction. After loss of the eyelash reflex, the lungs were ventilated with 100% oxygen. When BIS decreased below 70, a bolus alfentanil (0.02 mg/kg) and vecuronium bromide (0.1 mg/kg) were injected IV, after which the lungs were mechanically ventilated by laryngeal mask with a mixture of air/oxygen (40%: 60%). Propofol plasma concentrations were titrated to BIS values between 40 and 60 in order to maintain adequate hypnosis during surgery in general and during presentation of auditory stimuli in particular. Target concentration (in µg/ml) was adjusted in the following successive steps: 6 to 5 to 4.5 to 4 to 3.5 to 3 to 2.8 to 2.6 (and so on in steps of 0.2 µg/mL) and vice versa.

Study material

Experimental stimuli were similar to those used in two previous studies that demonstrated an implicit memory effect for four common exemplars of familiar word categories presented during general anesthesia (Jelicic et al., 1992; Roorda-Hrdlicková et al., 1990). In these studies, patients listened to the repeated recordings of yellow, banana, green, pear (experimental group) or to seaside sounds (control group), and were postoperatively asked to name the first three fruits and colors coming to mind. Without conscious recall, exemplars presented during anesthesia (i.e, hits) were generated significantly more often by patients in the experimental group. A large group difference was observed in the first study using this test (Roorda-Hrdlicková et al., 1990), with averages of 2.35 versus 0.79 hits (effect size d = 1.6). A replication study (Jelicic et al., 1992) resulted in a smaller, yet significant memory effect with averages of 2.4 versus 1.84 hits (d = 0.6). Given these effect sizes, the a priori probability to demonstrate a memory effect if a genuine difference between conditions exists, is between 0.84 and 1.00 when 41 patients are included in either group.

Accordingly, we randomly assigned patients to an experimental (E) or control (C) group and presented stimuli on audiotape from first incision onward. For group C, the tape contained 45 min of filler sound (birds singing). For group E, the tape started with filler sound (3 min) followed by the repeated recordings (15 min) of the four exemplars after which filler sounds continued. Target exemplars were recorded in a female voice (experimenter CK) at a speed of one word every 1.5 s, and series were repeated 30 times with 20 s silence in between repetitions. Tapes were coded by someone not involved in the experiment to ensure a double-blinded study.

Memory assessment

To assess memory for the intraoperative period in general and the four presented words in particular, patients were interviewed at the earliest convenient time after surgery. The interview assessed conscious recall of the surgical period by asking patients what they remembered ("What is the last thing you remember before you fell asleep?", "What is the first thing you remember after waking up?", "Do you remember anything in between?", and "Did you dream?"). This is also referred to as a direct or explicit memory test. Because memory may be implicit (unconscious), however, it is preferable to administer additional tests that do not require conscious recollection. Accordingly, we used a recognition test and category exemplar generation task. Both may reveal implicit memory effects provided that all items are responded to (Merikle & Daneman, 1996). The former is a less stringent test of implicit memory, however, because it makes reference to the learning episode (i.e., direct memory test) whereas the latter does not (i.e., indirect memory test).

After the interview, we administered the exemplar generation task and asked patients to name the first three exemplars coming to mind for the categories vegetables, fruits, and colors (in that order). Exemplar generation from the first category assessed whether groups responded similarly to a new category of which exemplars had not been presented to either group (control assessment). In contrast, exemplar generation from the latter two categories tested memory for exemplars presented to group E during anesthesia (experimental assessment). In the absence of conscious recall, implicit memory would be evident if group E generated more target exemplars than group C. Finally, word recognition was measured by reading out loud four exemplars from each category. For fruits and colors, these consisted of the two target exemplars presented to group E during anesthesia (banana, pear, yellow, green) and two exemplars that had not been presented to either group (apple, orange, red, blue). From each category, patients were instructed to choose one exemplar they possibly recognized from the anesthetic period, or to guess otherwise (4 alternative forced-choice). Recognition memory would be evident if patients in group E pointed out more target exemplars than patients in group C. In the absence of conscious recall, this would signal implicit memory.

Statistical analyses

Cluster analysis explored the multiple response set for vegetable exemplar generation in groups E and C. Chi-square tests were used to analyze observed frequency distributions (target exemplar generation and recognition, *gender, surgery type*), and Student's t-tests to analyze continuous data (*age; duration of surgery and anesthesia; amount of anesthesia, analgesia and muscle relaxant; average BIS during audio presentation; time between end of surgery and* test). A Bonferroni correction for multiple testing was applied to tests of patient characteristics (indicated in italic), dividing the usual level of significance ($\alpha = 0.05$) by the number of tests (10). For the remaining tests, $p < 0.05$ was considered statistically significant. Data are presented as mean ± SD.

Results

Patients (38 female, 44 male) were on average 35 ± 11 yr of age (range 18 - 61 yr) and underwent either orthopedic (n = 42), general (n = 29) or urologic (n = 11) surgery. The E and C groups were comparable on relevant patient characteristics (Table 1). None of the patients reported conscious recollection of the intraoperative period, nor were presented exemplars recognized more often by patients in group E (0.9 ± 0.8 hits) than in group C (0.8 ± 0.8 hits) ($p = 0.7$).

Table 1. Patient characteristics.

	Experimental group (n = 41)	Control group (n = 41)
Age (yr)	34 ± 10	36 ± 11
Men/Women (n)	25/16	19/22
Type of surgery (n)	$19^a/14^b/8^c$	$23^a/15^b/3^c$
Duration of surgery (min)	38 ± 28	34 ± 23
Duration of anesthesia (min)	59 ± 30	54 ± 23
Total dose propofol (mg)	750 ± 340	710 ± 280
Total dose alfentanil (mg)	1.2 ± 0.3	1.1 ± 0.3
Total dose norcuron (mg)	7.0 ± 2.1	6.6 ± 1.3
BIS during audio presentation	44 ± 4.6	46 ± 4.8
Time till test (min)	115 ± 32	110 ± 39

Values are mean ± SD or observed frequency. Means were compared using Student's t-test for two independent samples (experimental versus control group). Frequency distributions in groups were compared using Chi-square tests. All differences were statistically nonsignificant. BIS = Bispectral index; [a]orthopedic surgery, [b]general surgery, [c]urologic surgery.

To control for a priori group differences in task performance, patients generated exemplars from a control category (vegetables). Responses were effectively described by a two-dimensional solution, indicating that two main response clusters were discriminated: one predominated by common vegetable exemplars, the other by less common exemplars.

Individual patient loadings on either dimension indicated that both groups were equally inclined to generate common category exemplars. When asked to name exemplars from the experimental categories, group E generated 2.10 ± 1.0 hits compared to 1.98 ± 1.0 hits in group C ($p = 0.9$). Effect size (d) was 0.12.

A post hoc multiple linear regression analysis explored potential confounding of performance on the experimental category exemplar generation task. Hit scores consistently varied with duration of anesthesia ($r = 0.25$, $p< 0.05$) and type of surgery ($r = 0.33$ $p< 0.01$). Correlations indicated that more hits were generated after prolonged anesthesia, as well as after urologic (2.82 ± 0.9) and orthopedic (2.10 ± 1.0) surgery than after general surgery (1.66 ± 1.0). Anesthesia and surgery had a similar effect on performance in groups E and C. This is indicated by a largely unaffected regression weight (β, measure of validity and effect size) and SE (reflecting reliability) in the prediction of study group hit scores when covariates were ($\beta = 0.04$, SE = 0.11) or were not included ($\beta = 0.06$, SE= 0.11) in the regression model.

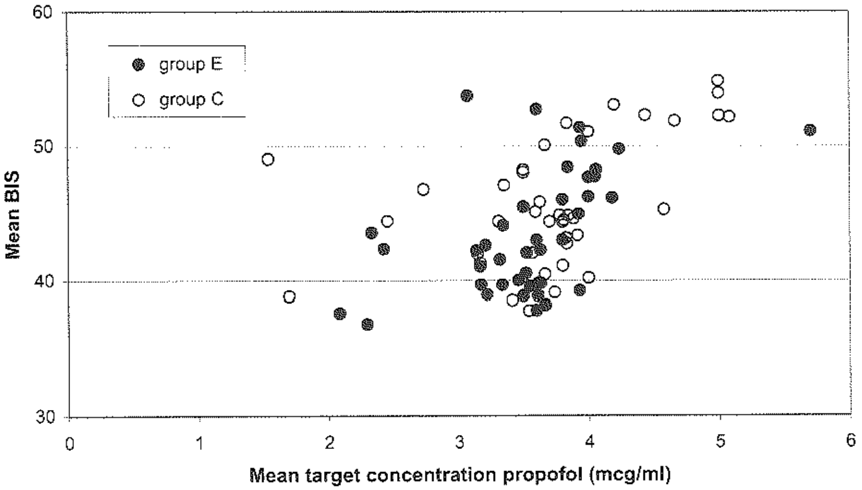

Figure 1. Bispectral index (BIS) in relation to targeted plasma concentration propofol during audio presentation in groups E (n= 41) and C (n= 41).

BIS monitoring

Propofol target concentration during audiotape presentation was 3.6 ± 0.6 μg/ml in group E and 3.7 ± 0.8 μg/ml in group C ($p = 0.3$), which resulted in clustering of hypnotic states near BIS 40 (Figure 1). As can be seen in Figure 2, an overall stable level of hypnosis was obtained during word presentation to patients in group E. Post hoc exploration of the relation between mean BIS during word presentation and target exemplar generation in group E revealed no decrease in hit scores with increasing hypnotic depth at this controlled level of hypnosis (BIS 55-50: 1.8 hits, n = 5; BIS 50-45: 1.9 hits, n = 9; BIS 45-40: 1.9 hits, n = 13; BIS 40-35: 2.6 hits, n = 14). No statistical analyses were performed because observations were unevenly distributed and limited in number.

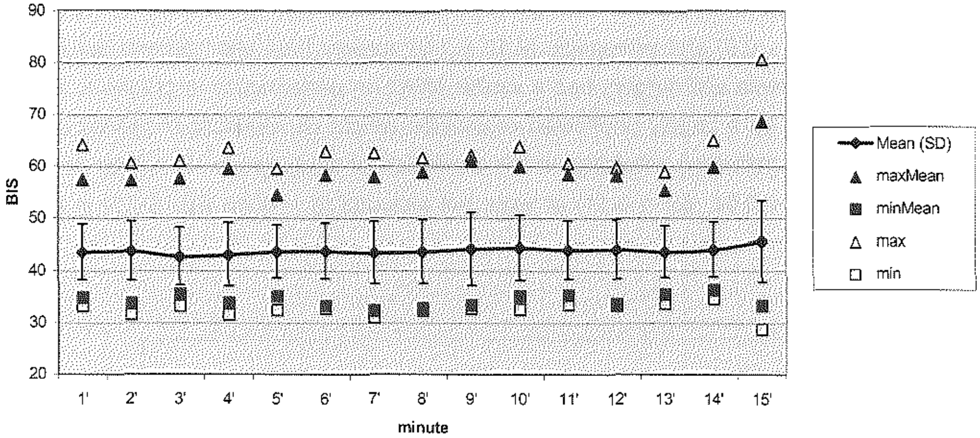

Figure 2. Bispectral index (BIS) during word presentation in group E (n= 41). For each minute, an average (Mean) over all BIS samples (n= 495) was calculated. The range of observations is indicated by the highest (max) and lowest (min) BIS value. In addition, an average BIS was calculated for each patient, the range of which is indicated by the highest (maxMean) and lowest (minMean) mean observed. Mean BIS values > 60 were observed in the 9th min (n = 2: M_1 = 60.5, M_2 = 61.1) and in the 15th min (n = 3: M_1 = 63.5, M_2 = 63.6, M_3 = 68.6).

Discussion

Implicit memory effects for auditory information presented during general anesthesia imply information processing during anesthesia. Because such effects may result from inadequate anesthesia, however, it is important to control level of hypnosis during stimulus presentation. This study used EEG-BIS to monitor hypnotic state continuously while a series of words were repeatedly presented to patients in the experimental group. More important, words were presented during adequate anesthesia only, reflected by BIS values between 40 and 60. Patients in the control group were anesthetized similarly but heard filler sounds instead. Implicit memory effects for presented words had been demonstrated in two previous, but similar, studies without controlling for hypnotic state (Jelicic et al., 1992; Roorda-Hrdlicková et al., 1990). Therefore, we used the same study material but presented stimuli under strict anesthetic monitoring to assess memory formation during controlled adequate anesthesia.

While the a priori probability to detect group differences was high using this particular paradigm, no memory effect was observed. Patients in the experimental group displayed no conscious recall and were unable to recognize presented category exemplars. In addition, they failed to generate more hits than the control group. Hence, no evidence of word priming during anesthesia was found. Given the small effect size in this sample, the probability of demonstrating an experimental effect was low in retrospect (power = 0.12). More specifically, our results indicate that words presented at BIS levels near 45 were not processed to the extent that memory could occur. This is in line with reports by Struys et al. (1998) who found no evidence of memory for auditory information presented at BIS levels between 40 and 60.

Because previous studies using the same stimuli (Jelicic et al., 1992; Roorda-Hrdlicková et al., 1990) demonstrated implicit memory effects without monitoring hypnotic state, the present null findings suggest diminished information processing when controlled adequate anesthesia is provided. At this controlled level, stimuli may be processed less elaborately or by fewer individuals, resulting in reduced stimulus processing in general and absence of memory formation. This notion is again supported by Struys et al. (1998) who found a lower (zero) incidence of implicit memory for BIS-guided anesthetics than for procedures monitoring classical signs of anesthetic adequacy. Our findings implicate that previous demonstrations of implicit memory (Jelicic et al., 1992; Roorda-Hrdlicková et al., 1990) may have come about by undetected moments of inadequate anesthesia, and stress the importance of maintaining stable levels of hypnosis during surgery and stimulus presentation in particular. Together, these observations support the feasibility of BIS as a monitor of adequate anesthesia without memory formation.

This notion is not consistent with the implicit memory effect found for words presented at BIS 40 to 60 in trauma patients (Lubke et al., 1999). Because that study included a wide range of hypnotic states (i.e., BIS 21 to 96), however, moments of lightened anesthesia might have affected results. In a similar vein, it should be noted that analyses were confined to words, i.e., relating the BIS level during word presentation to subsequent memory performance, thereby neglecting intraindividual variations in hypnotic state. Therefore, although a significant memory effect for words presented at adequate levels of hypnosis was found, effects of light anesthesia within the individual patient were not controlled for in the trauma study. In the present study and that of Struys et al. (1998) they were.

Second, differences in anesthetic regimen may partly explain controversial memory findings at equisedative levels of hypnosis. In the trauma study (Lubke et al., 1999), isoflurane was used for anesthetic maintenance whereas both Struys et al. (1998) and we used propofol, a reportedly effective agent in abolition of information processing and memory (Veselis, Reinsel, Feshchenko & Wronski, 1997; Veselis et al., 1992). A large multicenter study found no relation between anesthetic regimen and probability of recall, but curves for propofol and isoflurane appeared to have different slopes, suggesting different relations to memory (Glass et al., 1997). In particular, memory tended to occur earlier with isoflurane than with propofol. Because propofol may have contributed to the null findings, replication studies with other anesthetic agents are important.

A third explanation for the memory effect observed in trauma patients but not in elective surgical patients may be found in the type of surgery and associated level of stress. Elevated levels of stress hormones, e.g. epinephrine and cortisol, are known to modulate memory storage (Cahill & McGaugh, 1998). Trauma patients presumably are exposed to more stress than elective surgical outpatients, which may explain why memory has been observed in the former but not in the latter group of patients at adequate levels of hypnosis.

To summarize, the lack of evidence for explicit and implicit memory in this study suggests absence of memory formation when controlled adequate propofol anesthesia is provided. Maintaining stable levels of hypnosis seems crucial in this respect. Additional studies need to establish the reliability of our observations, especially so with anesthetics other than propofol.

3

Memory function during propofol and alfentanil anesthesia: predictive value of individual differences

Kerssens, Lubke, Klein, van der Woerd & Bonke (2002)

Abstract

Conscious recall and implicit memory have been shown to be dependent on hypnotic state as measured by EEG bispectral index (BIS). A third expression of memory (unconscious–controlled memory) was recently observed after moderate to light sedation (BIS 70 to 80). The present study investigated memory function during deep sedation (BIS 60 to 70). As memory effects are small, we studied potential predictors of individual differences in memory performance. Memory function and speed of information processing were assessed in 56 outpatients prior to surgery. During propofol anesthesia supplemented with alfentanil, patients heard a series of words while anesthesia was titrated to BIS 60 to 70. In between words, response to command was assessed using the Isolated Forearm Technique. We tested memory with a word stem completion task and process dissociation procedure to distinguish explicit from implicit effects. Mean (± SD) BIS during word presentation was 64.0 ± 3. Patients with conscious recall of verbal commands (n = 9) did not recall or recognize presented words. Even so, the process dissociation procedure revealed evidence of memory by a significantly higher hit rate in the inclusion condition (0.26) than in the exclusion condition (0.12). Patients without conscious recall showed no evidence of memory for presented words. Hit scores correlated significantly with scores in the preoperative memory test (r = 0.35). We found evidence of weak explicit memory function during anesthesia titrated to BIS 60 to 70. The observations strongly suggest that postoperative memory relates to awareness during anesthesia but the nature of this relation remains unclear. Memory seems more likely in patients with good preoperative memory performance.

Introduction

Research and understanding of memory function during anesthesia have substantially improved over the past few years. Electroencephalographic (EEG) bispectral index (BIS) has been introduced as an online monitor of hypnotic state allowing control of hypnotic adequacy (Johanson & Sebel, 2000; Rampil, 1998; Sigl & Chamoun, 1994). In addition, recent studies have clearly distinguished explicit (conscious) memory effects from implicit (unconscious) memory effects using the process dissociation procedure (PDP) (Lubke, Kerssens, Gershon & Sebel, 2000; Lubke, Kerssens, Phaf & Sebel, 1999; Stapleton & Andrade, 2000). With PDP, the assumption that different tests are exclusively sensitive to either explicit or implicit memory function is avoided and both memory processes are assessed within a single test (Jacoby, 1991; Jacoby, Toth & Yonelinas, 1993). PDP requires participants to perform under two different experimental conditions. In one (inclusion) condition, they are instructed to use previously presented information in their response, whereas such information should be avoided in the other (exclusion) condition.

Ability to follow these instructions reflects response control, a feature associated only with explicit memory function.

Conscious recall is the first type of memory suppressed with deepening hypnotic state and is unlikely to occur at BIS levels below 70 (Glass et al., 1997; Iselin-Chaves et al., 1998; Kerssens & Sebel, 2001; Liu, Singh & White, 1997). Implicit memory function seems to deteriorate less quickly and has been observed during adequate hypnosis (BIS 40 to 60) in one study (Lubke et al., 1999) but was not evident in two others (Kerssens, Klein, van der Woerd & Bonke, 2001; Struys et al., 1998). A third expression of memory was recently found for words presented at light levels of hypnosis (BIS above 70) during emergency cesarean sections (Lubke et al, 2000). Without conscious awareness, patients correctly included or excluded presented words and thereby displayed response control. This finding was referred to as unconscious-controlled memory, a weak form of explicit memory that can occur in the absence of conscious recall.

The present study was designed to investigate memory function during BIS 60 to 70. As in our previous studies (Lubke et al., 1999, 2000), we recorded BIS during word presentation and used a word stem completion test (WS test) in combination with PDP to assess memory. The overall small effect sizes in this area of research indicate that memory for specific information presented during anesthesia is a reliable yet uncommon phenomenon (Merikle & Daneman, 1996). Because individual characteristics may determine the probability (i.e., risk) of memory, the present study investigated preoperative memory function and speed of information processing as potential determinants of memory performance, as well as awareness during anesthesia with the Isolated Forearm Technique (IFT) (Russell & Wang, 2001; Tunstall, 1977).

Materials and Methods

Following approval from the human investigations committee at the Academic Hospital Rotterdam, the Netherlands, sixty-five healthy (ASA I-II) outpatients scheduled for surgery under general anesthesia gave written informed consent to participate and were enrolled in the study. Patients were between 18 and 60 years of age, fluent in Dutch and reported intact hearing and no history of drug abuse or current use of psychoactive medication.

The study comprised three phases. Several weeks prior to surgery, speed of information processing and memory function were assessed (preoperative phase). During anesthesia and before surgery commenced –in order to avoid the potentially confounding effect of noxious stimulation– patients listened to a series of words and verbal commands while anesthesia was maintained at BIS 60 to 70 (peri-operative phase). After surgery, memory for presented words and commands was tested (postoperative phase).

Preoperative assessments

Speed of information processing (SIP) was assessed with a choice reaction time task in which an arrow (black against white background, font: Geneva, size 72) appeared in the center of a Macintosh PowerBook 3400 computer screen (Apple Computers, Cupertino CA, USA) pointing either left or right. Participants were instructed to indicate the orientation of the arrow as quickly as possible by pressing a particular key. Stimuli remained visible until a response was generated with a maximum of 3 s. A new stimulus appeared after 1 s. Ten practice trials preceded 50 test trials. From the test trials, an average reaction time was derived for each individual, after removing incorrect responses and outliers (reaction time above or below 3 SD from the mean). The number of included test trials ranged from 43 to 50.

To assess individual memory function, patients were shown 10 printed words introduced as illustrative examples of what could be played during anesthesia. Half of the patients were shown list A, the other half list B. Patients were instructed to study and memorize all words for 1 min. Attention was then diverted (SIP-test) and approximately 5 min after study, memory was tested using a word stem completion task (MEM-test). Twenty printed word stems corresponding to the words of list A and B were shown. Participants were told that some of the stems could be completed to words from the study list. They were instructed to use stems as cue to recall studied words and to complete the stems accordingly, or to complete stems with the first word coming to mind in case recall failed. After completing all stems, patients were asked to point out the words the remembered from the study list. For each patient, we established the number of study words used for stem completion (*cued recall hits*) as well as the number of study words pointed out correctly (*recognition hits*).

Intra-anesthetic assessments

EEG activity was measured using an A1000 monitor (Aspect Medical Systems Inc., Newton MA, USA) with a two-referential montage. Four self-prepping electrodes (Zipprep; Aspect Medical Systems Inc.) were attached to the following sites: channel 1 and 2 to the left and right outer malar bone (At1 and At2), a referential electrode midway the forehead (Fpz) and a ground electrode approximately 2 cm right from the reference electrode (Fp2). Electrode impedance was below 5 kΩ during EEG recording. Recording of BIS (algorithm 3.2) started before induction of anesthesia and continued throughout the presurgical anesthetic period.

The anesthetic protocol consisted of target-controlled infusion (TCI) with propofol using an IVAC infusion pump (Alaris Medical Systems, San Diego CA, USA) targeting propofol plasma concentrations with Diprifusor software (AstraZeneca Macclesfield, Cheshire, UK). Patients received no premedication and anesthesia was induced with propofol, 6 µg/ml, TCI. After loss of the eyelash reflex, the lungs were ventilated with 100%

oxygen. A bolus alfentanil (20 µg/kg) was administered intraveneously when BIS decreased below 80, followed by suxamethonium (1 mg/kg) when BIS decreased below 60. The trachea was then intubated and the lungs were mechanically ventilated with a mixture of air:oxygen (60%:40%). When the train-of-four indicated return of muscular activity, a cuff was inflated to 250 mmHg around the forearm of the dominant hand, occluding blood flow to the hand. This isolated forearm technique (IFT) excluded the hand from neuromuscular block when vecuronium bromide (0.1 mg/kg) was injected, and enabled patients to indicate awareness either spontaneously or upon request (explained below). Propofol plasma concentration was targeted to BIS 60 to 70 for the remainder of the presurgical study period and word presentation started as soon as BIS was above 60.

The 44 words used in this study were selected after a pilot word stem completion study in a comparable group of patients (n = 30). The pilot established the probability of correct word stem completion without previous presentation of the corresponding word (i.e., base rate). Base rates of selected words ranged from 0.17 to 0.33 (mean = 0.25) and words were assigned to four lists so that comparable bases rate occurred. Each patient was presented with two lists during anesthesia (22 targets) and tested on all 44 words, including the two lists that had not been presented during anesthesia (22 distractors). Lists were counterbalanced so that all words appeared equally often as a target and as a distractor. Words were digitally recorded in a female voice (first author), saved as 16-bit sound samples and played to patients *via* closed headphones connected to a Macintosh PowerBook 3400 (Apple Computers, Cupertino CA, USA). A computer program generated a different random word order for each patient and repeated each target 10 times consecutively with a 1s delay in between repetitions. The ten repetitions of each target took about 35s. Using automatic data logging, the average BIS during the 35s word presentation was recorded. Observers were blinded to the contents of word presentation.

In between word presentations, i.e. after 10 repetitions of the same word, response to verbal command (i.e., awareness) was assessed. The computer program for word presentation was halted, headphones were partially lifted and the observer, who continuously held hands with the patient, spoke close to the patient's ear. Each command was preceded by the patient's name and followed by stroking the palm of the nonparalyzed hand. Patients were first asked to squeeze the observer's hand once. If no squeeze occurred within approximately 10s, responsiveness was scored absent (*nonresponse)* and word presentation continued. Patients who did squeeze once were then asked to squeeze twice. Failure to squeeze twice was considered an inadequate (*equivocal*) response and word presentation continued. Squeezing twice upon command was considered an adequate (*unequivocal*) response indicating awareness and we then asked patients to squeeze twice if they felt all right or to stretch their fingers if not. In the latter case, propofol infusion was increased with

0.2 or 0.5 µg/ml TCI depending on the going target concentration (below or above 3 µg/ml, respectively). If necessary, additional alfentanil (1 mg) was given. Before patients entered the operating room and surgery commenced, the anesthetic was increased until BIS 45, and the cuff, headphones and electrodes were removed.

Postoperative assessments

Within hours after surgery, patients were tested on the ward just prior to hospital discharge. We assessed conscious recall with a short structured interview consisting of the following four questions: "What is the last thing you remember before falling asleep?", "What is the first thing you remember after waking up?", "Do you remember anything in between?", and "Did you dream?" (Liu, Thorp, Graham & Aitkenhead, 1991).

The WS test was then administered in combination with the process dissociation procedure (PDP). PDP requires participants to complete a memory test under two different experimental conditions. In both conditions, subjects are presented with cues (e.g., word stem) serving recall of information (e.g., words) presented earlier (e.g., during anesthesia). In the inclusion condition, participants are instructed to complete stems with a word presented earlier or with the first word coming to mind in case recall fails. Because both explicit and implicit memory function lead to the same response (i.e., completion with the presented word), the inclusion condition is a measure of general memory performance. To separate explicit and implicit memory effects, the exclusion condition is required in which the instruction is given **not** to use presented words for stem completion but to use another word instead. Contrary to the inclusion condition, an explicit memory effect in the exclusion condition results in less frequent responding with presented words. Comparison of test scores in the two conditions indicates whether memory test performance should be attributed to implicit or explicit memory function and relative contributions of both may be estimated (Lubke et al., 1999, 2000; Stapleton & Andrade, 2000).

In line with the PDP, the WS test consisted of an inclusion and exclusion part, the order of which randomly varied between patients. Instructions were thoroughly explained before each part and illustrated with an example. Word stems were presented auditorily *via* closed headphones as well as visually on a computer screen, using the same headphones and computer as during word presentation. The digital sound sample of the word stem had been derived from the sound sample of the word presented during anesthesia, which had been copied and cut so that only the first few letters remained audible. For each patient, the computer program selected two word lists (1 target and 1 distractor) for the inclusion condition and exclusion condition each and presented the corresponding word stems in a different random order. Overall, each of the 44 words appeared equally often as a target and as a distractor in the inclusion and exclusion test condition. In each condition, patients completed 11 word stems corresponding to target words and 11 corresponding to distractors. Responses were entered into the computer by the observer.

As a measure of cued recall, patients were instructed to report each word they recalled hearing during anesthesia. They were reminded to do so once during and once after the inclusion and exclusion test part. Finally, all 44 words were read to patients in a fixed order and for each word, patients decided whether or not it had been played to them during anesthesia (recognition test).

Statistical analysis

The first part of data analysis focused on observed hit rates in the two conditions of the WS test, a hit representing responding with a study word. The distractor hit rate establishes the probability of responding with a study word without it being presented previously (i.e., base rate). The hit rate for targets, in contrast, establishes the probability of responding with a study word when it has been presented during anesthesia (i.e., hit rate). Paired samples t-tests were used to compare the hit rate to base rate in the inclusion and exclusion condition. Implicit memory function would lead to hit rates higher than base rate in both parts of the test. Explicit memory function, on the other hand, would result in a hit rate higher than base rate in the inclusion condition and a hit rate lower than base rate in the exclusion condition. This result evidences response control, a feature associated with explicit memory function only. Response control, however, may be observed in the absence of conscious recall (unconscious-controlled memory) or in its presence (conscious-controlled memory). Absence of memory is indicated by base rate performance in both the inclusion and exclusion parts of the WS test.

The second part of data analysis addressed individual differences in memory function during anesthesia using a linear multiple regression model with general memory performance as a dependent variable. Therefore, this part of the analysis was based on the data obtained in the inclusion condition of the WS test. Given the limited sample size, a restricted number of variables were studied as predictors (Stevens, 1992). Prior to surgery, patients' speed of information processing and memory function were investigated because good learning ability has been associated with quicker sensory processing (Deary, 1999; Roberts, Pallier & Goff, 1999) and better memory function (Hunt, 1999; Woltz, 1999). During surgery we assessed response to command because postoperative memory is often attributed to awareness. From these assessments we derived the (a) mean reaction time in the SIP-test, (b) number of cued recall hits and (c) recognition hits in the MEM-test, (d) percentages of equivocal and (e) unequivocal response to IFT command, and entered (a) to (e) as predictor variables in the regression analysis (SPSS 9.0, SPSS Inc., Chicago IL, USA). Only cases with observations for all 5 variables were included in the analysis. SPSS tested correlations between memory performance and predictor variables for 1-tailed significance, which is common for statistical testing of a priori (directional) hypotheses.

Thirdly, we performed an item-analysis. Despite careful memory test construction, not all words and word stems (i.e., items) in this study were expected to measure memory equally well. As malfunctioning items elicit unwanted variance thereby reducing statistical power, item-analysis was performed on the word stem completion data to identify and remove such items from the test. The aim was to improve the tests' overall quality. Using (SPSS) Scale Reliability Analysis, we identified 15 items that correlated poorly with other items regardless of a memory effect, i.e. based on the distractor data in the inclusion and exclusion conditions. These items also correlated poorly with other items in the target inclusion condition which measures memory. Removing these items from the test increased its internal consistency, as measured by Cronbach's alpha (Crocker & Algina, 1986, chap. 6), from 0.12 (44 items) to 0.43 (29 items) to 0.67 (24 items) after removing another five. Based on this improved version of the WS test, we calculated new hit scores for each patient and re-analyzed the memory effect and its relation to predictor variables as described above. $P < 0.05$ was considered statistically significant. Data are presented as mean ± SD.

Results

Nine patients were excluded from the data set, either because median BIS remained below 60 during word presentation (n = 5), or due to failure to complete memory testing (n = 4). Included patients (25 female, 31 male) were aged 37 ± 10 yr (range 19 – 58) and underwent either orthopedic (n = 45), general (n = 7) or plastic surgery (n = 4). They were anesthetized for 39 ± 11 min in the presurgical study period, followed by 45 ± 17 min of general anesthesia for surgery. The IFT was implemented for 24 ± 3 min during which words and commands were presented over a period of 19 ± 2 min. BIS during word presentation was 64.0 ± 3 and 1082 commands were given overall (average of 19 ± 3 per patient). No response was observed to 887 commands (82%), equivocal response to 56 commands (5%) and unequivocal response to 139 commands (13%). Fifteen patients (27%) did not respond to command at any time (309 nonresponses) whereas 37 patients (66%) responded unequivocally to command at some point during their anesthetic (range once to 16 times). Memory was assessed 3.8 ± 0.5 h after word presentation and 2.8 ± 0.5 h after surgery.

Memory Test Results

All patients were interviewed about conscious recall of peri-anesthetic events: nine (16%) reported partial yet accurate recall of verbal commands but no patient remembered any of the words presented in between commands. Presentation of word stems (cued recall test) resulted in 8 correct recollections *versus* 37 incorrect recollections overall. When memory was prompted even further by showing the target words mixed with distractors (recognition test), patients overall recognized 143 words correctly versus 140 incorrectly. These observations indicate absence of unprompted and prompted conscious recall for presented words.

Observed hit rates for target and distractors in the WS test are shown in Table 1. In the original WS test, the hit rate tended to be higher than base rate in the inclusion condition and lower than base rate in exclusion condition, but neither difference was statistically significant ($p = 0.25$ inclusion condition; $p = 0.13$ exclusion condition). When comparing the hit rates of the two test conditions, significantly more hits were scored in the inclusion part than in the exclusion part ($p < 0.05$). This indicates that patients did have memory for presented words. In the improved version of the WS test results were basically the same: hit rates differed significantly between test conditions ($p < 0.05$) but not from base rate within test conditions ($p = 0.09$ inclusion condition; $p = 0.33$ exclusion condition).

Table 1. Mean hit rates (SD) in the postoperative word stem completion test.

	Original Test		Improved Test	
List	Inclusion Condition	Exclusion Condition	Inclusion Condition	Exclusion Condition
Target	0.27 (0.15)^a	0.22 (0.13)^a	0.30 (0.25)^b	0.22 (0.18)^b
Distractor	0.25 (0.12)	0.25 (0.15)	0.24 (0.17)	0.24 (0.21)

A hit represents responding with a study word presented during anesthesia (target hit or hit rate) or not presented during anesthesia (distractor hit or base rate). In the inclusion condition, patients were instructed to use presented words for stem completion, in the exclusion condition they were instructed to avoid such words. The original test consisted of 44 items, the improved test was based on the results of an item-analysis and consisted of 24 items. Hit rates were calculated by dividing the observed number of hits by the potential number of hits (= number of patients × number of items in a particular condition). This table shows the probability of responding with a study word in each test condition. ^{a,b} $P < 0.05$

Because conscious recollection is a key aspect of the process dissociation procedure, we performed post hoc analyses on the word stem completion data of patients with and without conscious recall of verbal commands even though none of the participants remembered the words presented. As can be seen in Table 2, the hit rate of patients with conscious recall was significantly higher in the inclusion condition than in the exclusion condition ($p < 0.05$). No other comparisons reached statistical significance. Characteristics of the two groups (Table 3) indicated that patients with recall more often responded to IFT commands although BIS was comparable during such responses. Preoperative and postoperative performance were comparable as well.

Table 2. Mean hit rates (SD) for patients with and without conscious recall of commands.

	Recall (n = 9)		No Recall (n = 47)	
List	Inclusion Condition	Exclusion Condition	Inclusion Condition	Exclusion Condition
Target	0.26 (0.14)[a]	0.12 (0.12)[a]	0.27 (0.15)	0.24 (0.13)
Distractor	0.28 (0.10)	0.20 (0.10)	0.25 (0.12)	0.26 (0.16)

Because conscious recollection is an important feature of the process dissociation procedure, word stem completion performance of patients with and without conscious recall was separately analyzed on a post hoc basis. Note that none of the patients remembered or recognized the words used in this test. [a] $P < 0.05$

Table 3. Data of patients with and without conscious recall of verbal commands.

	Recall	No Recall	between-groups
age	36.6 (9.4)	37.0 (9.9)	p = 0.9
male / female	4M / 5F	27M / 20F	p = 0.5
reaction time SIP	414 (69)	394 (57)	p = 0.4
cued recall hits MEM	5.7 (1.7)	5.2 (1.9)	p = 0.5
recognition hits MEM	5.8 (2.8)	4.4 (2.8)	p = 0.3
BIS during words	65.4 (2.7)	63.7 (2.6)	p = 0.1
BIS during IFT+	67.6 (5.5)	67.1 (3.7)	p = 0.5
% IFT+	29.6 (23)	10.3 (13)	p < 0.05
cued recall hits WS	0.33 (0.7)	0.11 (0.3)	p = 0.4
cued recall FA WS	0.67 (0.7)	0.66 (1.1)	p = 1.0
recognition hits	3.89 (4.0)	2.35 (3.4)	p = 0.3
recognition FA	3.22 (4.3)	2.41 (4.0)	p = 0.6

Data are presented as mean (SD) or observed frequency. Age is shown in years, reaction time in milliseconds. SIP = speed of information processing test (preoperative). MEM = memory test (preoperative). BIS = bispectral index (during anesthesia). IFT+ = unequivocal responding to verbal command using the isolated forearm technique (during anesthesia). WS = word stem completion test (postoperative). Hit = responding with a study word. FA = false alarm or false positive (incorrect response). Hits and FA are displayed as observed relative (mean) frequency.

Individual Differences

Thirty-eight patients were included in the regression analysis, which aimed at predicting WS test performance from preoperative and intra-anesthetic variables. In the remaining 18 patients, preoperative assessments were not obtained. Because conscious recall turned out to be an important variable, it was added as predictor in the analysis. Results for the original and improved versions of the WS test were comparable and, for informative purposes, the strongest correlations are reported here. No significant correlations were found between postoperative hit scores and preoperative recognition hits (r = 0.25), choice reaction time (r = -0.19), percentages of equivocal (r = 0.24) or unequivocal (r = 0.06) response to command, and conscious recall (r = 0.03). Hit scores did correlate significantly to the number of hits produced in the preoperative memory test (r = 0.35, $p < 0.05$). As can be seen in Figure 1, this correlation was particularly strong in the recall group (r = 0.61, n = 6) compared to the no-recall group (r = 0.29, n = 32) but neither was statistically significant (p = 0.1 and p = 0.06, respectively). Taken together, the regression model explained 13% to 15% of the variance in postoperative hit scores (original vs. improved WS test).

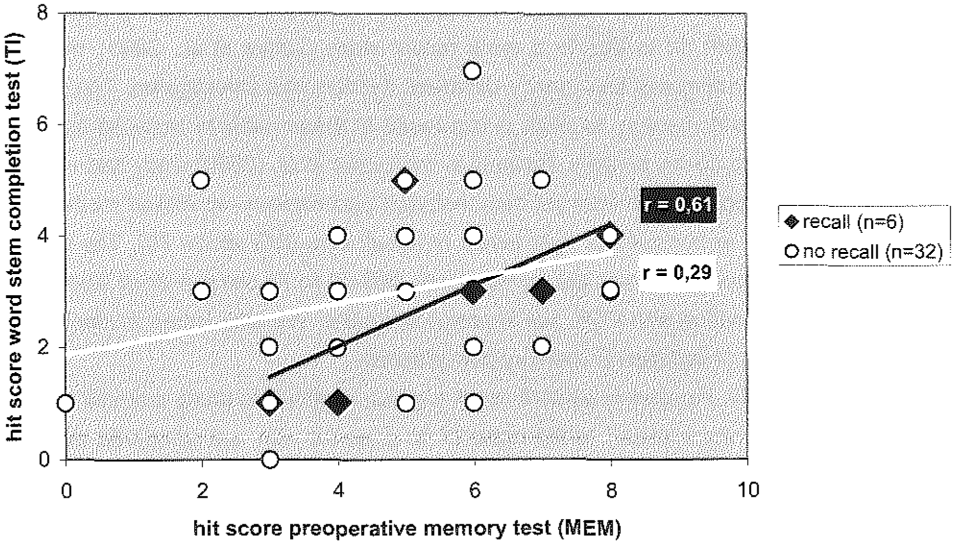

Figure 1. Correlation (r) between preoperative and postoperative memory test performance. This figure illustrates the regression analysis (N = 38) in which preoperative memory performance served as a predictor variable (X-axis) of postoperative memory performance (Y-axis). A hit in the preoperative memory test means that a word stem was completed to a word studied a few minutes earlier. A hit in the postoperative test means that a word stem was completed to a word presented during anesthesia. The latter scores were based on the inclusion condition of the test because we were interested in general memory performance (see also Statistical Analysis). Because conscious recall affected postoperative memory performance, results are separated between patients with and without conscious recall. The overall correlation was 0.35 ($p < 0.05$).

Discussion

Memory function during anesthesia has been studied for different (physiological, psychological, medico-legal) reasons and with mixed results (Andrade, 1995; Ghoneim & Block, 1992, 1997). Much research was hampered by a lack of control for anesthetic adequacy and for long, memory tests were thought to reflect either conscious (explicit) or unconscious (implicit) learning. Recent technological and methodological advances have improved reliable measurement of hypnotic adequacy and memory function during anesthesia. BIS was introduced as an online index of hypnotic state ranging from 100 (awake) to 0 (isoelectric brain) and PDP enabled separation of explicit from implicit memory effects within a single test (Jacoby, 1991; Jacoby et al., 1993).

Using both BIS and PDP, we (Lubke et al., 1999) have demonstrated dependence of memory function on hypnotic state in acute trauma patients undergoing surgery at different levels of anesthesia, as well as preserved implicit memory function during apparently adequate hypnosis (BIS 40 to 60). In a more recent study (Lubke et al., 2000), memory function in women undergoing emergency cesarean section was investigated. The probability of awareness and memory function is increased in these patients because hypnotic state is generally light during surgery. Patients in the Lubke et al. (2000) study had no conscious recall of intraoperative events yet demonstrated unconscious–controlled memory for the words presented at consistently light levels of anesthesia (BIS above 70). The current study assessed memory for words presented during BIS 60 to 70 using a word stem completion task in combination with PDP, like in previous studies. We also aimed to identify patient–related sources of variation in memory performance.

Conventionally, memory is evident when a group exposed to study material outperforms another group not exposed to the material. In a similar vein, we compared target to distractor hit rates in both conditions of the WS test. In the inclusion condition, patients were inclined to use a study word more often for stem completion when it had been presented during anesthesia than when it had not. In the exclusion condition, in contrast, they tended to use fewer presented words when instructed to avoid those. These observations suggest explicit memory for presented words but a conventional memory effect was not found. This is in line with the absence of conscious recall and recognition of presented words seen in this study.

Patients did make correct inclusion–exclusion decisions, however, as evidenced by the higher hit rate in the inclusion condition compared to that in the exclusion condition. Thus, they displayed response control over words presented on average at BIS 64. Because none of the words was consciously recalled or recognized, decisions to either include or exclude a word were made without conscious awareness. Hence, we found evidence of unconscious–controlled memory. This finding corroborates the results of Lubke et al. (2000)

who presented words at BIS levels consistently above 70 during emergency cesarean sections. As response control is typically associated with explicit memory function (Jacoby, 1991) but was not accompanied by conscious recall, Lubke et al. (2000) concluded that unconscious-controlled memory is a weak form of explicit memory. Our current findings extend the evidence of weak explicit memory function to a near-adequate level of hypnosis. Lubke et al. (2000), however, demonstrated response control in addition to a conventional memory effect. Therefore, their evidence of weak explicit memory function was stronger than in the present study. This is also indicated by effect size estimates (h) for response control in the previous and present studies (h = 0.31 vs. 0.13). The stronger evidence found by Lubke et al. (2000), in combination with an on average higher BIS during cesarean section supports dependence of memory function on hypnotic state as measured by BIS.

It should be noted that only patients with conscious recall demonstrated response control and as such, the evidence of weak explicit memory function in the present study should be attributed to this particular group of patients. No reliable effect was found in patients not reporting recall. This difference between patients supports the process dissociation procedure in that the presence or absence of conscious recall leads to differential response patterns. Unlike most PDP experiments with awake subjects, however, our studies show that the ability to exclude is not necessarily accompanied by conscious awareness and recollection. None of our patients, including those with recall of commands, remembered or recognized the words presented during anesthesia. They were nevertheless able to include or exclude words. From a clinical point of view, the difference in word stem completion performance between patients with and without conscious recall is also relevant because it indicates unconscious consequences of intra-anesthetic awareness. Those with recall unknowingly "act" differently. Our findings strongly suggest that such awareness affects postoperative memory but the relation is not straightforward, as illustrated by the fact that only one in four patients responding to command during anesthesia reported conscious recall afterwards.

Using PDP, Stapleton and Andrade (2000) also observed reliable explicit memory in the absence of conscious recall. Whereas they were not convinced that such findings should be treated as special, we tend to go along the lines of Lubke and Sebel (2000), arguing that the dichotomy between conscious recall and implicit memory is too crude. Instead, a third expression of memory should be distinguished that incorporates both implicit and explicit features. Unconscious–controlled memory is implicit in terms of conscious recollection, which is absent, but explicit in terms of response control, which is present.

Stapleton and Andrade (2000) did not measure BIS during word presentation but determined blood concentrations propofol after presenting a word list during surgery and assessed response to command at the start and end of the list. Neither index of depth of anesthesia correlated with memory performance and the authors expressed confusion over these findings as "explicit memory is typically very sensitive to manipulations of consciousness". We too found awareness during anesthesia to be of little predictive value to memory performance apart from recall. Our observations and those of Stapleton and Andrade (2000) could be well explained taking the experience of being awake during anesthesia into account. Some of our patients accurately recollected awareness but none remembered the words presented within seconds before of after the commands. Although ethical considerations confine the scope of memory research to relatively unimportant words, the current findings suggest that painful experiences, conversations about life-threatening issues or fearful events such as awakening paralyzed are a more memorable stimulus than simple (neutral) words. Our patients expressed concern over what had been happening while being awake rather than remembering or paying attention to the words. Hence, responsiveness may be expected to correlate poorly with memory performance for presented words.

Predicting variation in memory performance was partially successful. On the one hand, preoperative memory performance correlated with postoperative hit scores, a finding interesting in two respects. Whereas preoperative hit scores had predictive value, recognition memory did not. This might indicate that implicit rather than explicit memory function affects memory formation during anesthesia, although no attempts were made to separate the two in the preoperative memory test. Furthermore, because this correlation could be demonstrated in a relatively small sample, the study of presumably stable (internal) patient characteristics, as opposed to transient (external) variables like depth of anesthesia, is a potentially promising field of research. On the other hand, preoperative hit scores explained 12% (R^2) of the variance in postoperative hit scores, leaving a large proportion of variance unexplained. The predictive value was even weaker in patients without conscious recall, who constituted the main part of our study sample. Furthermore, the difference between patients with and without conscious recall is unfortunately left unexplained by this study. Beside awareness during anesthesia, no other indicator discriminated between the groups.

In summary, decisions to use or avoid words presented during anesthesia in a postoperative word stem completion test can be made without conscious recall or recognition of presented words. This corroborates a previous finding of unconscious-controlled memory for words presented at consistently light to moderate sedation as measured by BIS and extends the evidence of weak explicit memory function to a near-adequate level of hypnotic state. Our results are consistent with the hypothesis that memory performance depends on hypnotic state during word presentation and suggest unconscious influences of awareness during anesthesia. Memory function may be predicted by stable patient characteristics such as memory function before surgery. Finally, awareness seems an important predictor of conscious recall but the relation between these two phenomena is not straightforward.

4

Awareness: monitoring versus remembering what happened

Kerssens, Klein & Bonke (accepted for publication in Anesthesiology)

Abstract

Awareness during anesthesia is an unacceptable complication that is foremost assessed with postoperative interviews. The sensitivity of interviews is questionable whereas intra-operative monitors, such as BIS and responsiveness to command, are not necessarily commonly used. This study investigated response to command during deep sedation (BIS 60 to 70) and the ability of novel monitoring techniques to indicate awareness and predict recall. We systematically assessed response to command using the isolated forearm technique (IFT) while monitoring electroencephalographic and hemodynamic variables. Fifty-six elective surgical patients were repeatedly given verbal instructions to squeeze the observer's hand during target-controlled propofol anesthesia supplemented with alfentanil. After recovery, conscious recall was assessed with a short structured interview. Overall, 1082 commands were given. No response was observed to 887 (82%) commands, equivocal response to 56 (5%) commands, and unequivocal response to 139 (13%) commands. Of the 37 patients (66%) with unequivocal response to command (awareness), nine (25%) reported conscious recall after recovery. Hemodynamic variables poorly predicted awareness, whereas EEG-derived parameters, especially BIS, were highly significant predictors ($p < 0.0001$). EEG parameters did not discriminate between patients with or without conscious recall, whereas heart rate and responsiveness did. The incidence of awareness is underestimated when conscious recall is taken as evidence. Awareness can be monitored online with behavioral and modern neurophysiological measures. Providing feedback during intra-anesthetic awareness helps patients cope with a potentially stressful situation.

Introduction

Regaining consciousness during alleged general anesthesia ("awareness") is a frightening experience, that often causes patients to panic and feel helpless even when no pain is experienced (Moerman, Bonke & Oosting, 1993). It is not necessarily the awakening itself that is most distressing to patients but the inability to move or communicate, which gives rise to feelings that the worst is yet to come. Unpleasant aftereffects of awareness are not uncommon and include insomnia, recurrent nightmares, emotional distress and posttraumatic stress disorder (Domino, Posner, Caplan & Cheney, 1999; Moerman et al., 1993; Osterman & van der Kolk, 1998).

With an increasing number of formal complaints filed and granted (Domino et al., 1999), awareness is an unacceptable complication. Monitoring awareness is complicated, however. Ideally, the monitor is a measure of consciousness sensitive to the individual patient. EEG-derived parameters, such as bispectral index (BIS) or spectral and median frequency (SEF; MF), discriminate between consciousness and unconsciousness (Kerssens & Sebel, 2001) but remain probabilistic in nature. Using a data base as a reference model, these measures are imperfectly sensitive to the individual state of mind and substantial variation between patients at comparable levels of hypnosis may be observed. Hemodynamic, respiratory, muscular and autonomic signs, on the other hand, are nonspecific indicators of cognitive change and do not reliably indicate consciousness (Schneider & Sebel, 1997). The auditory evoked potential is a promising tool derived from EEG responses in the individual brain, but has only scarcely been used and studied during anesthesia. Its clinical utility therefore remains uncertain.

Another way to monitor awareness is the evaluation of response to command. When neuromuscular blocking drugs are given, the isolated forearm technique (IFT) can be used (Tunstall, 1997). The IFT entails inflation of a pneumatic cuff around one arm (to ± 250 mmHg) before muscle blockade is induced, and thus prevents the hand from being paralyzed. Studies using the IFT have shown that the incidence of awareness, as indicated by purposeful movement of the hand, is underestimated when conscious recall is taken as evidence (Russell, 2001) and illustrate the limited usefulness of postoperative interviews when it comes to awareness monitoring. Nonetheless, interviews remain the hallmark of clinical practice and research (Ghoneim, 2000; Sandin, Enlund, Samuelsson & Lennmarken, 2000).

As part of a randomized-controlled study of memory function during deep sedation (BIS 60 to 70) induced and maintained with propofol and alfentanil (Kerssens, Lubke, Klein, van der Woerd & Bonke, 2002), we assessed response to command with the IFT while monitoring EEG and hemodynamic variables. Based on a large number of observations, this paper reports on the merits of traditional and modern techniques to monitor intra-anesthetic awareness, and on the feelings of patients who consciously recalled awareness. In addition, we explored the usefulness of prevailing monitoring techniques in prediction of postoperative conscious recall.

Materials and Methods

After approval from the human investigations committee at the University Medical Center Rotterdam, the Netherlands, 56 healthy (ASA I-II) outpatients scheduled for orthopedic (n = 45), general (n = 7) or plastic surgery (n = 4) under general anesthesia consented to be included in the study. Patients (25 female, 31 male) were aged (mean ± SD) 37 ± 10 yr (range 19–58), fluent in Dutch and reported intact hearing and no history of drug abuse or current use of psychoactive medication. In order to avoid the potentially confounding effect of noxious stimulation, anesthesia was induced 30 min prior to surgery. During this presurgical study period and while hypnotic state was maintained at BIS 60 to 70, we assessed wakefulness while recording common parameters of anesthetic adequacy. After conclusion of the study period, hypnotic state was deepened to BIS 45 (approximately) and surgery started. After recovery, memory was assessed using a short structured interview.

Electric activity of the brain was measured using an A1000 monitor (Aspect Medical Systems, Newton MA, USA) with a two-referential montage. Four self-prepping electrodes (Zipprep: Aspect Medical Systems) were attached to the following sites: channel 1 and 2 to the left and right outer malar bone (At1 and At2), a referential electrode midway the forehead (Fpz) and a ground electrode approximately 2 cm right from the reference electrode (Fp2). Electrode impedance was below 5 kΩ during EEG recordings. The following data were automatically and continuously recorded throughout the presurgical anesthetic period: BIS, SEF, MF, all every 5s, heart rate (HR) and mean arterial blood pressure (MAP) every 5 min.

The anesthetic procedure was standardized and consisted of target-controlled infusion (TCI) with propofol using an IVAC infusion pump (Alaris Medical Systems, San Diego CA, USA) with Diprifusor software (AstraZeneca Macclesfield, Cheshire, UK) targeting plasma concentration propofol. Patients received no premedication and anesthesia was induced with propofol, 6 µg/ml, TCI. After loss of the eyelash reflex, the lungs were ventilated with 100% oxygen. When BIS decreased below 80, a bolus alfentanil (20 µg/kg) was injected intravenously followed by succinylcholine (1 mg/kg) when BIS decreased below 60. The trachea was intubated and the lungs were mechanically ventilated with a mixture of air and oxygen (60%:40%). When the train-of-four indicated return of muscular activity, a cuff was inflated to 250 mmHg around the forearm of the dominant hand. This isolated forearm technique (IFT) prevented the hand from being paralyzed when vecuronium (0.1 mg/kg) was subsequently administered. Propofol plasma concentration was targeted to BIS 60 to 70 for the remainder of the presurgical period.

At regular intervals, approximately once every 50 s, the observer (first author) determined awareness in terms of response to verbal command. Each command started with the patient's first name and was followed by stroking the palm of the nonparalyzed hand. Patients were first asked to squeeze the observer's hand once. If no squeeze occurred within approximately 10s, responsiveness was scored absent (*nonresponse)*. Patients who did squeeze once were then instructed to squeeze twice. Failure to squeeze twice was considered an inadequate (*equivocal*) response whereas squeezing twice was considered an adequate (*unequivocal*) response, indicating awareness. In these instances, we asked patients to squeeze twice again if they felt alright or to stretch their fingers if not. When patients indicated they were uncomfortable, propofol infusion was increased with 0.2 or 0.5 µg/ml TCI, depending on the going target concentration (below or above 3 µg/ml, respectively). If necessary, additional alfentanil (1 mg) was given. Before patients entered the operating room, propofol infusion was increased until BIS was approximately 45 and the cuff, headphones, and electrodes were removed.

On the ward just prior to hospital discharge, patients were interviewed about conscious recall with the following four questions: "What is the last thing you remember before falling asleep?", "What is the first thing you remember after waking up?", "Do you remember anything in between?", "Did you dream?" (Liu, Thorp, Graham & Aitkenhead, 1991).

Data analysis

Because the incidence of awareness during anesthesia and postoperative conscious recall were unknown a priori, facts and feelings about awareness were explored on a post hoc basis. Feelings were assessed by questioning patients who reported recall in closer detail (e.g., what do you remember, how often were you given a command, how did you feel?). Facts about awareness were addressed by associating the three types of response to command with recordings of EEG and hemodynamic variables. Automatic data logging allowed each response to be associated with a mean value for BIS, SEF, MF, HR, and MAP. We analyzed whether these parameters monitored awareness and discriminated between nonresponses and unequivocal responses to command with a random regression model for dichotomous data, using the Generalized Estimating Equation (GEE) method to estimate prediction performance of each parameter. Because data were obtained from repeated measurements (longitudinal data), observations were considered not to be independent, which standard regression analysis requires. GEE allows modeling of longitudinal data because it takes the correlated nature of such data into account (Zeger & Lang, 1992). Using Statistical Analysis Systems (SAS 6.2) software, BIS, SEF, MF, HR and MAP were entered as covariates of nonresponse versus unequivocal response to command. $P < 0.05$ was considered statistically significant and data are presented as mean ± SD.

Results

Patients were anesthetized for 39 ± 11 min in the presurgical study period, followed by 45 ± 17 min of general anesthesia for surgery. The IFT was implemented for 24 ± 3 min during which commands were given over a period of 19 ± 2 min. A total of 1082 commands were given (19 ± 3 per patient). No response was observed to 887 commands (82%), an equivocal response to 56 commands (5%) and an unequivocal response to 139 commands (13%). Fifteen patients (27%) did not respond to command at any time, whereas 37 patients (66%) responded unequivocally at some point during their anesthetic (range: once to 16 times).

EEG and hemodynamic measurements during the three types of response to command are shown in Table 1. For informative purposes, this table also shows the traditional

EEG power bands (delta, theta, alpha, and beta). Because band powers are of limited utility for anesthesia-related applications (Rampil, 1998) and are not used as parameter of hypnotic adequacy in the field, they were not taken into consideration for statistical analysis. When the other parameters (BIS, SEF, MF, HR, and MAP) were simultaneously included in the regression analysis, none discriminated between unequivocal response and nonresponse. When each parameter was entered separately, however, all except HR predicted awareness. The latter observation combined with the former indicated that parameters shared predictive characteristics (i.e., multicollinearity), which is not surprising given the mutual (central nervous system; autonomic nervous system) origin of these measures.

Table 1. EEG and hemodynamic variables during three types of response to command.

	nonresponse (n = 887)	equivocal (n = 56)	unequivocal (n = 139)
% DELTA power	**25.0** ± 13.6	**22.5** ± 14.7	**13.3** ± 8.3
	(24.1 – 25.9)	(18.6 – 26.5)	(11.9 – 14.7)
% THETA power	**10.4** ± 4.0	**9.3** ± 3.1	**7.1** ± 2.9
	(10.2 – 10.7)	(8.5 – 10.2)	(6.6 – 7.6)
% ALPHA power	**33.1** ± 9.4	**31.1** ± 8.1	**27.9** ± 9.2
	(32.4 – 33.7)	(28.9 – 33.3)	(26.3 – 29.4)
% BETA power	**31.5** ± 13.5	**37.0** ± 13.4	**51.7** ± 13.9
	(30.6 – 32.4)	(33.4 – 40.6)	(49.4 – 54.1)
Spectral Edge Frequency	**20.3** ± 2.1	**21.7** ± 1.9	**22.7** ± 2.0
	(20.2 – 20.5)	(20.6 – 21.6)	(22.4 – 23.0)
Median Frequency	**10.7** ± 2.7	**10.7** ± 2.6	**13.1** ± 2.5
	(10.5 – 10.9)	(10.0 – 11.4)	(12.7 – 13.6)
Bispectral Index	**63.2** ± 4.9	**64.3** ± 4.3	**67.3** ± 4.4
	(62.9 – 63.5)	(63.1 – 65.4)	(66.5 – 68.0)
Heart Rate	**68.1** ± 11.6	**68.0** ± 12.1	**69.4** ± 13.6
	(67.3 – 68.8)	(64.7 – 71.3)	(67.0 – 71.9)
Mean Arterial Pressure	**84.3** ± 16.3	**89.5** ± 14.8	**88.8** ± 17.1
	(83.2 – 85.4)	(85.5 – 93.6)	(85.7 – 91.9)

Data are presented as mean ± SD (95% confidence interval Mean). Power refers to the amplitude (μV) of EEG waveforms, which typically fall into one of four frequency bands: delta (0.5 to 3.5 Hz), theta (4.0 to 7.75 Hz), alpha (8.0 to 13.5 Hz), and beta (13.75 to 30 Hz). In general, high frequency waveforms of low amplitude characterize an awake, conscious brain.

A slightly different approach was therefore adopted, by consecutively analyzing all (10) combinations of 3 parameters. The overall pattern of results showed that HR never predicted awareness. MAP was a significant predictor ($p < 0.01$) when HR was excluded from the analysis, but in these cases EEG measures always yielded stronger predictors ($p < 0.0001$). When HR and MAP were included together with an EEG measure, neither predicted awareness in contrast to a highly significant EEG predictor. BIS, SEF, and MF all performed well ($p < 0.0001$) although MF lost its predictive value when SEF was simultaneously included in the analysis. This suggests that SEF is a better predictor than MF. When BIS, SEF, and MF were simultaneously compared, only BIS predicted awareness reliably ($p < 0.05$).

Conscious recall was assessed in all patients 2.8 ± 0.5 h after recovery from anesthesia. When asked whether they remembered anything in between falling asleep and waking up, nine patients (16%) reported recalling verbal commands. Table 2 summarizes their memories.

Table 2. Patients with conscious recall of verbal commands given during anesthesia.

M/F	age	number of unequivocal responses	number of commands recalled	Recollection
M	46	4	4	Squeeze hand. I felt alright, no panic. Wanted to talk.
M	43	16	10	Squeeze hand and how I felt, then I fell asleep. It felt alright.
F	30	0	0	My name and how I felt, a lot of questions. It felt alright.
F	33	2	3	My name, squeeze hand. I wanted to talk but couldn't. I wasn't afraid but felt closed in and a little awkward.
M	29	5	3	My name, squeeze hand. I had trouble to understand it was about me. Distress over responding, whether I succeeded.
F	41	3	3	Stretch fingers, remark "look, she stretches her fingers". I tried to respond but was not sure whether I succeeded. It felt alright.
M	23	7	4	Squeeze hand. No sense that I squeezed but understood that I succeeded. Not frightened but feared feeling pain. Glad to hear I was getting more anesthetic.
F	32	4	3	You called out but I couldn't respond. Wanted to, but my arm didn't go. Later sensed that it moved, then I fell asleep. Not afraid but I worried that you would think I was asleep and surgery would start.
F	52	10	6	Name, squeeze hand, a lot of questions. Felt alright, not afraid.

Foremost, all nine patients with conscious recall felt at ease postoperatively. Looking back, five clearly expressed having felt fine during the awareness episode. One patient had felt "closed in" and two had feared experiencing pain or the start of surgery. Being told what was happening and what they could expect had been a great relief, these patients reported. In dealing with the commands, three patients indicated that they had wanted to respond verbally but noticed they were unable to (without understanding why, the interviews suggested). Another patient reported having had trouble to understand that he was being addressed, and felt distressed over whether he complied with the commands. Similar distress over responding was expressed by two others, which suggests that their proprioception was distorted during sedation anesthesia. As our patients indicated, feedback from the outside world may fill the gap between the intention to move and the internal, subjective perception of movement. Finally, it should be recognized that conscious recall of commands closely matched the number of times patients had responded (Table 2, Pearson correlation = 0.96).

Because only one in four patients responding to command reported conscious recall, we explored sources of variation in patients with recall (n = 9) and those without (n = 47). Preoperative data, reported elsewhere (Kerssens et al., 2002), did not reveal differences between groups. Intra-anesthetic parameters during unequivocal responding to command are displayed in Table 3 for the two groups.

Table 3. Characteristics of patients with and without conscious recall of commands.

	Recall (n = 9)	No Recall (n = 47)	Independent Samples t-test
number of commands	18.9 ± 2.9	19.3 ± 3.0	$p = 0.7$
% non response	63.7 ± 23.2	84.4 ± 17.0	$p < 0.01$
% unequivocal response	29.6 ± 22.8	10.3 ± 12.6	$p < 0.05$*
% DELTA power	15.0 ± 10.2	12.3 ± 6.9	$p = 0.1$
% THETA power	7.4 ± 3.3	7.0 ± 2.6	$p = 0.5$
% ALPHA power	27.4 ± 10.1	28.1 ± 8.7	$p = 0.7$
% BETA power	50.2 ± 16.6	52.6 ± 12.1	$p = 0.4$
Spectral Edge Frequency	22.7 ± 2.0	22.7 ± 1.9	$p = 0.9$
Median Frequency	13.1 ± 3.2	13.1 ± 1.9	$p = 1.0$
Bispectral index	67.6 ± 5.5	67.1 ± 3.7	$p = 0.6$
Heart Rate	72.9 ± 16.1	67.4 ± 11.7	$p < 0.05$
Mean Arterial Pressure	87.0 ± 15.5	89.8 ± 17.9	$p = 0.3$

Data are mean ± SD. *Equal variances not assumed, $p < 0.01$ if equal variances assumed. Unequivocal responding was observed 51 times in patients with conscious recall and 88 times in patients without conscious recall. For heart rate and blood pressure, slightly fewer observations (n = 44 recall group; n = 77 no recall group) were obtained due to occasional unsuccessful data prompting.

Patients with conscious recall more often responded unequivocally to command, and likewise, were less often found not to respond. In addition, an increased heart rate was observed in patients with conscious recall. No other clinical parameter discriminated between groups.

Discussion

Preventing awareness is a key issue in clinical anesthesia and much effort has been directed in recent years towards developing a reliable monitor of anesthetic adequacy. Because the brain is the target effect site of anesthetics, several measures have evolved around electroencephalograhic activity. Whereas spectral edge and median frequency are derived from power (amplitude) analysis of the EEG, bispectral index also incorporates synchronization of brain waves (phase coupling) into its calculation. Monitors such as these are based on the notion that amplitude and synchronization increase with deepening sleep or hypnotic state. BIS, SEF and MF have been found to predict consciousness with much better accuracy than hemodynamic variables like heart rate and blood pressure. Prediction probabilities are not yet perfect, however, and variation in accuracy has been noted (Kerssens & Sebel, 2001).

Behavioral methods to monitor awareness include assessing responsiveness to (verbal, tactile, noxious) stimuli during anesthesia, and/or assessing conscious recall after recovery questioning. Perhaps because the former method appears awkward to both patients and clinicians, the postoperative interview is most frequently adhered to when it comes to awareness monitoring. The validity of this method is questionable, however, given the imperfect relation between awareness and memory. In general, less is remembered than is consciously perceived. During anesthesia, this notion has been demonstrated compellingly in studies using the isolated forearm technique assessing response to verbal command (Russell, 2001). Nonetheless, interviews remain the hallmark of awareness monitoring.

In order to optimize awareness monitoring during deep sedation (BIS 60 to 70), the present study combined behavioral and electroencephalographic measures. Response to command during anesthesia was associated to corresponding EEG and hemodynamic recordings, and conscious recall was assessed after recovery with a short structured interview. Approximately two-thirds of patients (37 in 56) responded to command at this particular level of hypnosis, some patients consistently so, but only one in four responding patients recollected episodes of awareness (9 in 37). By monitoring awareness during anesthesia and postoperatively, we demonstrated how the incidence of awareness is underestimated when conscious recall is taken as evidence and underline the limited usefulness of postoperative interviews. Therefore, if we want to attain awareness of awareness (Simini, 2000), it should be recognized that postoperative interviews are insufficiently sensitive to intra-anesthetic awareness, not unlikely because recollection decays as time passes and/or anesthetics drugs interfere with memory consolidation. Given the accuracy of recollection demonstrated by our patients, we emphasize that interviews are valuable and important but of limited value in detecting awareness.

If we want to detect awareness and deal with it while we can, the anesthetized patient is to be monitored. One way to achieve this is to assess response to command, requiring the isolated forearm technique (IFT) when muscular blocking drugs are used. The IFT has been criticized as a routine and effective monitor (see Russell, 2001, for a review), foremost because it could not be used for a prolonged period of time, and because responses would be difficult to interpret. A modification of the technique (Russell, 1979), however, allows the IFT to be used for longer surgical procedures, and asking for conditional responses can ascertain that the correct type of (unequivocal) response is manifest. Merely recording hand movement does not suffice (Russell & Wang, 1996). Although awkward, talking to an anesthetized patient allows the clinician to determine awareness accurately in each individual patient, and to provide reassuring feedback. As our study suggests, such feedback may alter any memories patients have and potentially reverses the observed relation between delayed neurotic symptoms and the inability of patients to understand what happened during undesired wakefulness (Sandin et al., 2000). In dealing with awareness and accompanying neurotic symptoms, Simini (2000) recently raised the question whether the possibility of awareness should be discussed with patients preoperatively or whether doing so would worry too many patients unnecessarily. In the present study, awareness was explicitly discussed as part of the informed consent procedure. Many patients expressed fear of waking up during surgery, and although initially confused, most felt reassured by our proposed precautions to signal awareness, knowing it would not go unnoticed.

Novel neurophysiological techniques provide for other means to monitor awareness online. Given that consciousness is a (higher) cortical function, it is not surprising that EEG indices were found to predict awareness better than autonomic signs. Furthermore, given that bispectral index incorporates more characteristics of the EEG into its calculation than spectral indices like SEF and MF, it not surprising that BIS discriminated best between consciousness and unconsciousness. With a large number of behavioral and EEG-related observations, our findings corroborate what previous studies have suggested (see Kerssens & Sebel, 2001, for a review) and strongly support the validity of BIS, as well as SEF, to monitor awareness during sedation and general anesthesia. Even though the relatively new monitoring techniques are not 100% sensitive, a critique raised by skeptics of recent technological advances (e.g., O'Connor et al., 2001), they predict awareness more accurately than most commonly used, traditional indices. Given the serious after-effects of undesired wakefulness, caution over the sensitivity of awareness monitoring may not be in the best interest of our patients.

With respect to prediction of postoperative recall, only heart rate and responsiveness to command discriminated between patients with and without conscious recall. Given that heart rate is a reportedly unreliable indicator of recall (Moerman et al., 1993), the increased heart rate in patients with conscious recall must perhaps be attributed to distress. As indicated by the interviews, the systematic evaluation of response to command worried patients over whether or not they would succeed in responding. Rather than being indicative of postoperative conscious recall, therefore, increased heart rate may have arisen due to our instructions. Furthermore, the minor difference in heart rate of patients with and without conscious recall casts doubt on its clinical value as a predictor of conscious recall, especially since clinical signs are not judged uniformly by anesthesiologists (Moerman et al., 1993).

Of the various EEG parameters, none discriminated between patients with and without conscious recall. This underlines the notion that BIS and parameters alike were developed, and are suitable, for monitoring awareness during anesthesia but not necessarily memory function. BIS was similar for patients with and without conscious recall, while the former group responded more often to command. This demonstrates that some patients are more responsive to stimulation than others at equisedative levels of anesthesia, suggesting that a subgroup of patients is perhaps prone to perception during anesthesia. As responsiveness related to conscious recall, it is worthwhile to direct future attention toward denominating features of patients with awareness and conscious recall, in order to identify those at risk.

We conclude that it is important to monitor awareness intraoperatively or its prevalence is underestimated. Our data show that modern, online measures of hypnotic state, such as BIS and SEF, are useful instruments in this respect. Conscious recall is not necessarily indicated by these parameters and is best predicted by patient responsiveness to verbal command during anesthesia. The possibility of awareness can be openly discussed with patients in advance provided that an effort is made to detect wakefulness intraoperatively. Acknowledging awareness whenever it occurs and providing comforting feedback may reduce delayed neurotic symptoms.

5

Memory and affective priming during adequate propofol anesthesia monitored by electroencephalogram bispectral index

Kerssens, Klein & Bonke (submitted)

Abstract

In laboratory studies, affective reactions (e.g., preferences) are easily induced by repeated exposure to stimuli, especially for stimuli not consciously perceived. Preferences may be further affected by the prior occurrence of an emotionally arousing event (affective priming). Patients during anesthesia do not seem susceptible to emotional stimuli, but studies may have used too complex and indirect methods. We therefore adopted a simple, laboratory paradigm to study emotion and its effect on memory function. While anesthesia was titrated to BIS 40 and 60 (adequate hypnosis), 38 elective surgical patients were repeatedly played nonsense and relatively familiar (real) words, both with and without an emotionally positive sound (affective priming vs. control condition). After recovery, patients rated target and distractor words for evoked pleasure on a 6-point scale, and performed a memory task. Average ± SD BIS was comparable during the affective priming and control conditions (47.3 ± 11 vs. 45.8 ± 8.5). Word stem completion performance revealed similar hit probabilities for targets (0.22 ± 0.09) and distractors (0.24 ± 0.13), and affective priming of targets made no difference ($p = 0.5$). Ratings for primed nonsense words (3.34 ± 0.70) were comparable to those for unprimed words (3.31 ± 0.71) and distractors (3.25 ± 0.74). Insignificant differences were also observed for the real word set (4.07 ± 0.63; 4.13 ± 0.75; 4.16 ± 0.59, respectively). We found no evidence of emotional information processing or affect modulation during propofol anesthesia titrated to BIS 40 to 60 in elective surgical patients.

Introduction

Memory function during anesthesia has foremost been demonstrated for stimuli that lack emotional content or meaning. Having conducted a meta-analysis of studies, Merikle and Daneman (1996) concluded that such stimuli are both perceived and remembered as indicated by direct and indirect measures of memory. Studies in which an attempt was made to separate conscious from unconscious contributions to memory performance further suggest that memory effects need not necessarily arise from inadequate anesthesia but may also be attributed to unconscious processing of stimuli (Bonebakker et al., 1996; Lubke, Kerssens, Phaf & Sebel, 1999). The notion of unconscious perception may explain why preserved processing of simple word stimuli has been observed during general ("adequate") anesthesia as monitored by EEG bispectral index (BIS) (Lubke et al.,1999), even though other studies have failed to observe memory function at this level of anesthesia (Kerssens, Klein, van der Woerd & Bonke, 2001; Ouchi, Sebel & Kerssens, 2002; Struys et al., 1998).

The evidence for processing of emotionally relevant stimuli during anesthesia, on the other hand, is less convincing. While such stimuli bear more strongly on clinical matters, they are less frequently the subject of thorough investigation and have yielded mixed results. Therapeutic (positive) suggestions, for instance, do probably not have a beneficial effect on postoperative recovery (Merikle & Daneman, 1996). This suggests that emotional information processing is not preserved during general anesthesia, which is in line with two studies using a fear conditioning paradigm in humans (Ghoneim, Block & Fowles, 1992) and rats (Dutton et al., 2002).

The notion of preserved non-emotional information processing as opposed to attenuated processing of emotional information contrasts sharply with priming studies in the laboratory. These have shown that simple affective reactions (e.g., preferences) are easily induced by mere exposure to stimuli, in particular when subjects lack conscious awareness of the stimulus due to very brief (i.e., suboptimal) exposure durations (Bornstein, 1989). Furthermore, preferences of novel, ambiguous stimuli may be enhanced or attenuated by presentation of a potent affective stimulus (e.g., a picture of a happy or angry face) prior to it. Such affective priming has only been found in suboptimal priming conditions whereas non-emotional priming effects were much stronger after conscious (optimal) stimulus exposures. These laboratory studies suggest that during anesthesia processing of emotional information is more likely than non-emotional information processing (Murphy, Monahan & Zajonc, 1995; Murphy & Zajonc, 1993).

We therefore adopted an affective priming paradigm using a simple emotionally relevant sound and a direct measure of affect (preference) to investigate emotional information processing during general anesthesia titrated to BIS 40 to 60. The overall lack of evidence for such processing so far may perhaps be explained by the use of too complex emotional stimuli (e.g., sentences with therapeutic content) and indirect assessment of effect by using duration of hospitalization and analgesic requirement as outcome measures. Such stimuli may not *work* under anesthesia because they require a high level of analysis (Greenwald, 1992), and even if they do, their effect easily remains undetected if one uses outcome measures that are sensitive to a wide range of other variables.

Materials and Methods

With approval from the local human investigations committee, forty-three healthy (ASA I-II) outpatients scheduled for elective surgery under general anesthesia gave written informed consent to be enrolled in the study. They were between 18 and 65 years of age, fluent in Dutch, and reported intact hearing and no history of drug abuse or current use of psychoactive medication. Five patients were excluded from the data-set because anesthesia was maintained with sevoflurane instead of propofol (n = 4) or no muscular blocking drugs were given (n = 1), which may interfere with the EEG-measurement. The remaining 38 patients were (mean ± SD) 39 ± 11 yr of age and underwent orthopedic (n = 24), urologic (n = 10) or general (n = 4) surgery.

Anesthetic technique

Apart from pre-emptive analgesia (Voltaren 100mg supp), patients received no premedication. Nineteen patients were given intravenous anesthesia according to protocol, consisting of propofol induction (1.5 to 2.5 mg/kg) supplemented with a bolus alfentanil (6 to 10 μg/kg) and vecuronium bromide (0.1 mg/kg) to enable intubation with laryncheal mask (n = 27) or endotracheal tube (n = 11). Anesthesia was thereafter maintained with propofol. Two patients received fentanil (1-2 μg/kg) instead of alfentanil, thirteen were given rocuronium (0.5 to 0.6 mg/kg) instead of vecuronium bromide, and four received a combination of both.

After induction and loss of the eye-lash reflex, the lungs were ventilated with 100% oxygen and muscular blocking drugs were administered followed by analgesic drugs. After intubation, the lungs were mechanically ventilated with a mixture of air:oxygen (60%:40%) and propofol infusion started at a rate of 10 mg/kg/h using a standard infusion pump. During surgery, and auditory stimulus presentation in particular, hypnotic state was targeted to BIS 40 to 60 and anesthetics were titrated accordingly. Towards the end of surgery, propofol infusion was discontinued and the lungs were ventilated with 100% oxygen. The endotracheal tube or laryncheal mask was removed when patients responded to command to open their eyes.

Throughout the anesthetic procedure, we measured EEG activity with an A1000 monitor (Aspect Medical Systems Inc., Newton MA, USA) and a two-referential montage. Four self-prepping electrodes (Zipprep; Aspect Medical Systems Inc.) were attached to the following sites: channel 1 and 2 to the left and right outer malar bone (At1 and At2), a referential electrode midway the forehead (Fpz) and a ground electrode approximately 2 cm right from the reference electrode (Fp2). Electrode impedance remained below 5 kΩ during BIS (algorithm 3.2) recordings. As soon as BIS was at target level and ideally after first incision, auditory stimulus presentation started using a Macintosh Powerbook 3400 (Apple Computers, Cupertino, CA) and closed headphones.

Stimulus material

Patients were repeatedly presented with three types of stimuli during anesthesia: an emotional sound, relatively familiar Dutch words and nonsense words. The sound served to prime the words affectively and was derived from the International Affective Digitized Sounds (IADS) set developed by Bradley & Lang (1999). Of the twenty reportedly pleasant IADS sounds, we selected five to serve as an affective prime in the present study: Baby Laugh (sound # 110), Applause (# 351), Erotic Couple (# 215), Baseball (# 353), and Beethoven (# 810). These sounds reliably induced a highly pleasant feeling and moderate to high self-rated arousal in both male and female subjects in the Bradley and Lang (1999) investigation. To serve as affective primes, the 6-s sounds were imported into SoundEdit

16.2 for Macintosh, cut so that the first 4 s remained audible, and saved as 16-bit sound samples. Prior to induction of anesthesia, each patient listened to all five sounds and chose the one (s)he most preferred.

The relatively familiar word set comprised 24 Dutch words for which we previously found a memory effect after presenting the words during deep sedation (BIS 60 to 70) anesthesia with propofol, using a word stem completion task (Kerssens, Lubke, Klein, van der Woerd & Bonke, 2002). In order to replicate that study, we created four lists of six words each and presented patients with two of the lists during anesthesia (i.e., 12 targets) and tested them on all four lists, thus including those not been presented (12 distractors). Lists were counterbalanced so that each word appeared both as a target and as a distractor. In our previous study, the probability of correct word stem completion without presentation of the corresponding target word during anesthesia was 0.24 (range 0.17 to 0.30). This probability establishes chance performance, also referred to as base rate completion. For descriptive purposes, this word set is referred to as real words.

In line with an affective priming paradigm, we also included a set of nonsense words. Such stimuli are particularly suitable for investigating emotional reactions in terms of preference because they are novel and lack intrinsic emotional meaning. To assure that words evoked little emotion by themselves, a pilot study was conducted in a comparable group of patients (N = 23) who recovered from ambulatory surgery under general anesthesia at our institution. We created a set of nonsense, but Dutch-like, words by replacing two consonants with two unusual ones in 49 existing five-letter words (e.g., BOTER – MOZER). As for the real word set, the nonsense words were digitally recorded in a female voice (first author) with a 44,100 Hz sampling frequency in SoundEdit 16.2, saved as 16-bit sound samples, and were played to participants via closed headphones connected to a portable computer (Macintosh PowerBook 3400). In the pilot, each word was auditorily repeated once and also shown on a computer screen. Immediately after hearing/seeing the word, participants rated to what extent it evoked a pleasant feeling using a 6-point Likert rating scale with a graphic figure at both ends (after Bradley & Lang, 1999): a smiling, happy figure to the right to indicate 'very much' and a frowning, unhappy figure to the left to indicate 'not at all'. The scale was printed on an index card given to subjects to their aid. The observer entered ratings in the computer as scores between 1 (not at all) and 6 (very much).

After rating evoked pleasure (*valence*), participants indicated to what extent a nonsense word resembled an existing Dutch word. For this purpose, they used a similar 6-point rating scale with only the words *very much* to the right and *not at all* to the left. This scale was printed below the valence rating scale described above and ratings were entered similarly by the observer. Valence of the nonsense words overall varied between 1.95 and 3.04, resemblance from 1.29 to 2.89. The two correlated strongly (r = 0.81) possibly indicating that more familiar words evoked a more pleasant feeling. Based on this preliminary study, we selected 18 words that least resembled existing Dutch words to form the nonsense word set (mean ± SD Resemblance = 1.69 ± 0.79; Valence = 2.21 ± 0.93) and evenly assigned words to three lists of comparable valence. Patients in the actual study were presented with two of the lists, randomly chosen, during anesthesia (12 targets) and tested on all three, thus including the one not presented (6 distractors).

Finally, the pilot established to what extent the real word set evoked a pleasant feeling in order to create lists of comparable valence (M ± SD Valence = 4.24 ± 0.73). For this purpose, participants were auditorily and visually presented with all 24 words in random order and rated evoked pleasure with the same rating scale as used for the nonsense words.

Procedure

In the study during anesthesia, words were presented under two conditions in each subject (see Figure 1). Patients were first repeatedly presented with a series of nonsense and real words without affective prime. This established the *no-prime* (control) *condition* and assessed whether preferences were induced during general anesthesia by mere exposure to stimuli. Because such an emotional reaction can occur quite naturally for stimuli, irrespective of their emotional content, this condition could not establish whether an emotional stimulus or information is processed during anesthesia. In a second condition, therefore, a different series of nonsense and real words were presented in combination with an affective sound (*prime condition*) in order to assess whether preferences are reinforced by presenting an emotional stimulus in addition to the repeated exposure to the words. Where both conditions may result in increased word preference, only the latter indicates emotional stimulus processing. To avoid "contamination" of the control condition by the affective priming condition, the control condition came first.

In the no-prime condition, twelve words (6 neutral, 6 nonsense) were repeatedly presented using the same computer and headphones as in the pilot. A computer program randomly selected a neutral and a nonsense wordlist for each patient and presented words auditorily in a mixed, random order. Each word was presented 10 × consecutively with a 3-s delay in between repetitions after which a new series of words followed. In total, word presentation in the no-prime condition lasted 8 min.

For the prime condition, the computer program selected different neutral and nonsense wordlists, and presented these twelve words (6 neutral, 6 nonsense) together with the sound that patients had chosen before induction of anesthesia. This sound preceded each word presentation in the prime condition. As in the no-prime condition, words were presented 10 × consecutively after which a new series of words followed. In total, word presentation in the prime condition lasted 10 min.

	Real word set (n = 24)				Nonsense word set (n = 18)		
	List 1	List 2	List 3	List 4	List 5	List 6	List 7
group A (n = 10)	Tp	Tnp	D	D	Tp	Tnp	D
group B (n = 9)	D	Tp	Tnp	D	D	Tp	Tnp
group C (n = 9)	D	D	Tp	Tnp	Tnp	D	Tp
group D (n = 10)	Tnp	D	D	Tp	Tp	Tnp	D

Figure 1. Study design. Patients were randomly assigned to one of four groups (A to D) that were all presented with four word lists during anesthesia (Targets; T). Two of the lists comprised relatively familiar Dutch words (Real word set) and two lists contained nonsense words (Nonsense word set). Furthermore, one list of either word set was presented in combination with a positive sound in order to prime the words affectively (Tp), and likewise two lists were presented without affective prime (Tnp). Patients were tested on all seven lists, thus including the ones not presented during anesthesia (Distractors; D).

Testing

Within hours after surgery, patients were tested at the recovery ward. We assessed conscious recall with a short structured interview: "What is the last thing you remember before falling asleep?", "What is the first thing you remember after waking up?" "Do you remember anything in between?", and "Did you dream?" (Liu, Thorp, Graham & Aitkenhead, 1991).

Patients then completed a word stem completion task in order to assess memory for the real word set presented during anesthesia. The test included word stems corresponding to the 6 primed and 6 unprimed target words, in addition to 12 distractor stems corresponding to words not presented. All stems appeared consecutively on a computer screen and were, at the same time, auditorily presented twice *via* closed headphones, with a 1-s silence interval, using the same computer and headphones as during word presentation. To familiarize patients with the task, they first practiced with five word stems unrelated to the target and distractor words. For the test itself, patients were instructed to use the word stems as a cue for recalling words presented during anesthesia and to complete the word stems accordingly. We correctly informed patients that some of the stems could be completed to words presented during anesthesia whereas others could not. Patients were instructed to use the first word coming to mind for stem completion in case recall failed. The computer program then generated the 24 relevant word stems for each patient in random order. The observer entered the patients' responses into the computer.

Subsequently, patients rated the nonsense and real word sets for evoked pleasure (in random order). For each word set, the computer program selected the appropriate lists (Figure 1) and presented words visually and auditorily (twice) with a 1-s interval. Patients were instructed to indicate to what extent the words evoked a pleasant feeling and encouraged to respond spontaneously. They used the same 6-point graphic rating scale as in the pilot, with a smiling, happy figure to indicate 'very much', and a frowning, unhappy figure to indicate 'not at all'.

Statistical analysis

Two factors varied systematically within subjects across the real and nonsense word sets: words had either been presented during anesthesia or not (factor Word type) and presented words had either been affectively primed or not (factor Affective priming). Because affective priming applied to target words only, three conditions were created in both the word stem completion- and affective rating tasks: primed targets, unprimed targets, and distractors.

The word stem completion task included the set of real words, and stems completed to one of the 24 study words were scored as a "hit". The number of hits (i.e., hit frequency) served as the dependent variable for this task, assessing memory for words presented during anesthesia. A memory effect would be evident if hit frequency for targets exceeded that for distractors, which represented base-rate completion. In addition, a Word type × Affective priming interaction was expected as memory is generally stronger for affective stimuli than for neutral stimuli. We thus expected more hits in the word stem completion task for primed targets than for unprimed targets, and least for distractors .

The affective rating task included both the real and nonsense word sets (in separate sessions) and assessed an affective priming effect during anesthesia. Here, obtained ratings served as the dependent variable. We expected higher ratings for primed targets than for unprimed targets due to affective priming. Because repeated exposure to stimuli by itself may enhance positive affect (mere exposure effect), ratings for unprimed targets were expected higher than for distractors. Thus, for both the nonsense and real word sets, we expected higher affect ratings for primed targets than for unprimed targets, and lowest for distractors.

Differences in hit numbers and affect ratings for primed targets, unprimed targets and distractors were analyzed with a General Linear Model for repeated measurements using SPSS 10.0 software. $P < 0.05$ was considered statistically significant. Data are presented as mean ± SD.

Results

Patients (24 male, 14 female) remained a period of 59 ± 40 min (range 25 – 150) under anesthesia for surgery. The giggling sound of a baby most often served as affective prime (n = 20; 14 males, 6 females), followed by a piece of classical music (n = 13; 6M, 7F) and a stadium roar during a baseball game (n = 5; 4M, 1F). BIS during presentation of primed targets (47.3 ± 11 overall: $\text{BIS}_{\text{real words}} = 47.1 \pm 10.5$; $\text{BIS}_{\text{nonsense words}} = 47.4 \pm 11.4$) was similar to BIS during unprimed targets (45.8 ± 8.5 overall: $BIS_{real\ words}$ = 45.4 ± 8.2; $BIS_{nonsense\ words}$ = 46.2 ± 8.7). Due to inadvertent fluctuations in hypnotic state, 23% of words was presented at $BIS < 40$, 69%at BIS between 40 to 60, and 8% at $BIS > 60$. Percentages were similar for the two word sets in both priming conditions.

Patients completed the interview and tests 2.4 ± 0.8 h after recovery from anesthesia. The interview indicated absence of conscious recall for surgery and words presented during anesthesia. The word stem completion test revealed comparable hit probabilities for targets (0.219 ± 0.09) and distractors (0.243 ± 0.13) ($p = 0.3$), and no significant differences were found when taking affective priming of targets into account (Table 1).

Table 1. Number of hits and hit probability in the word stem completion test for primed targets, unprimed targets and distractors.

	primed target (n = 228)	unprimed target (n = 228)	distractor (n = 456)
number of hits	53	47	111
hit probability ± SD	0.232 ± 0.14	0.206 ± 0.15	0.243 ± 0.13

The relation between BIS during word presentation and hit probability in the word stem completion task (Figure 2) was such that hit probability for primed real words slightly increased as BIS increased, whereas the opposite was observed for unprimed real words. The reference line reflects chance performance and equals the distractor hit probability (0.243). Although these figures nicely illustrate our data, it must be recognized that BIS during word presentation did not reliably predict hit probabilities in the word stem completion task ($\beta_{primed\ words} = 0.004$, $p = 0.8$) ($\beta_{unprimed\ words} = -0.04$, $p = 0.1$). Distinguishing between deep ($BIS < 40$), adequate (BIS 40 to 60) and light ($BIS > 60$) hypnosis, Table 2 shows the number of hits observed at each level. Testing these numbers against chance performance, we observed significantly fewer hits for unprimed real words presented at BIS between 40 to 60 ($p < 0.05$). For primed real words, no such difference was found.

Table 2. Number of hits (hit probability) for primed and unprimed targets in the word stem completion test for three categorized BIS levels during word presentation.

	BIS < 40	BIS 40 to 60	BIS > 60
primed targets	11 (0.220)	37 (0.238)	5 (0.217)
unprimed targets	18 (0.316)	28 (0.178)*	1 (0.071)

Of all primed targets (n = 228), 50 were presented at BIS below 40, 155 at BIS between 40 to 60, and 23 at BIS above 60. For unprimed targets (n = 228), these numbers were 57, 157, and 14, respectively. *$p < 0.05$ compared to the distractor hit probability (= 0.243, see Table 1).

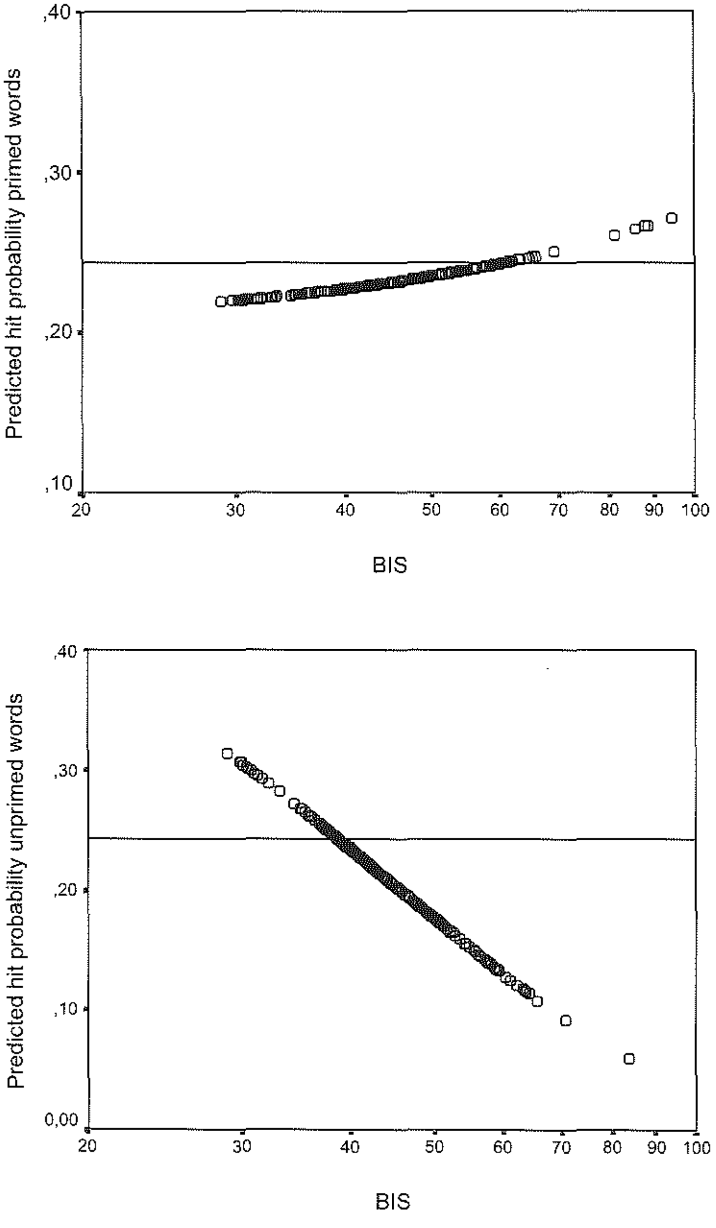

Figure 2. Predicted probability of hits in the word stem completion task as a function of BIS during presentation of real words that were affectively primed (top panel) and real words not primed (lower panel). The number of observations equals 228 (38 patients × 6 words) in both representations.

Affect ratings were in general more positive for relatively familiar Dutch words (grand mean = 4.12, $CI_{95\%}$ = 3.94 to 4.30) than for nonsense words (grand mean = 3.30, $CI_{95\%}$ = 3.09 to 3.50), as also observed in the pilot. Within the real word set, affect ratings were somewhat lower for primed targets (4.07 ± 0.63) than for unprimed targets (4.13 ± 0.75) and distractors (4.16 ± 0.59) but not significantly so ($p = 0.8$). A reverse tendency was observed for the nonsense set, but again our manipulation of affectively priming words (mean rating = 3.34 ± 0.70) versus repeated exposure without affective priming (3.31 ± 0.71) versus no exposure at all during anesthesia (3.25 ± 0.74), yielded no effect ($p = 0.6$). Surprisingly, blood pressure during presentation of nonsense words was related to postoperative affect ratings of both primed ($\beta = 0.22$, $p < 0.01$) and unprimed ($\beta = 0.17$, $p < 0.05$) words (see Figure 3). No such relation was found for the real word set or any of the other physiological parameters (BIS, spectral and median frequency, heart rate) that were registered during word presentation and entered as predictor variables in a regression analysis of affect ratings.

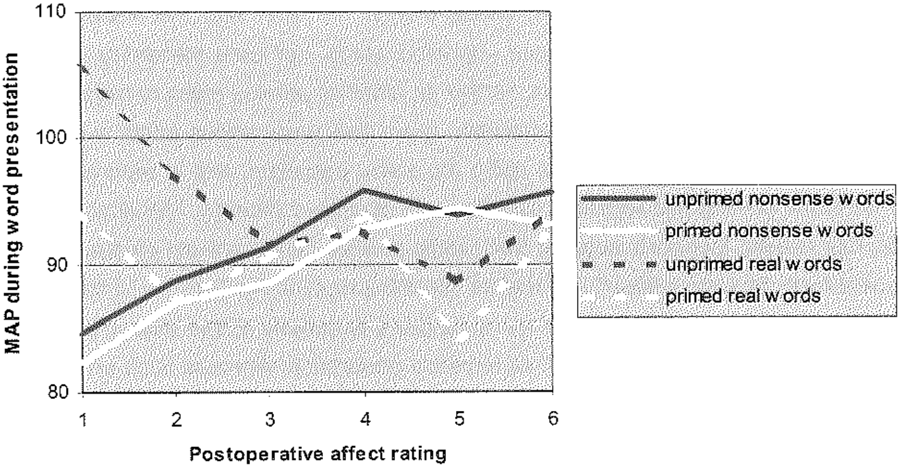

Figure 3. Postoperative affect ratings in relation to mean arterial pressure (MAP) during intra-anesthetic word presentation.

Discussion

This study investigated memory and affective priming during propofol anesthesia titrated to BIS 40 to 60. At this level, often referred to as adequate anesthesia, no evidence for information processing has been found in elective surgical patients (Kerssens et al., 2001; Ouchi et al., 2002; Struys et al., 1998). Although recent studies controlled for hypnotic state during stimulus presentation, which is an important issue in this field of research, the stimuli are typically of low salience and clinical relevance. Simple words, carefully selected to serve as auditory stimuli during anesthesia, have been used, or sentences embedding the words for which memory will be assessed. Such stimuli are vital to sound investigations of human cognition under anesthesia, but have little in common with real life surgical theater and may underestimate the incidence of auditory information processing during anesthesia. But how can one study salient events within common ethical limits?

The present study adopted an affective priming paradigm from laboratory studies of emotion to investigate processing of emotional information during general anesthesia. This type of processing seems particularly strong in unconscious stimulus conditions and may be preserved during adequate hypnosis. If enhanced memory performance and a change in feelings after a simple affective manipulation during anesthesia is demonstrated, this would imply that patients do process, and are influenced by, emotional information. Until then, information processing seems unlikely at this level of anesthesia and it is unclear what to expect from therapeutic suggestions presented during surgery.

Ironically, we found no evidence of emotional information processing but a perhaps spurious effect of information not affectively primed. To start with the former, patients displayed no preference of primed over unprimed words, nor were presented words preferred over not-presented words. Thus, neither an affective priming effect or mere exposure effect was demonstrated. This is remarkable, given that unconscious affect is easily and reliably induced in laboratory studies using the same paradigm, and is reportedly strong when affective priming and repeated exposure are combined (Murphy, Monahan & Zajonc, 1995). Our results, therefore, suggest that simple positive stimuli are not processed during adequate hypnotic state induced and maintained with propofol. Furthermore, it appears that unreinforced affect modulation due to mere exposure is unlikely at this level of anesthesia. Repeated presentation of stimuli did not increase preference, whereas such an effect has been demonstrated with nonsense words (Block, Ghoneim, Sum Ping & Ali, 1991). In that particular study, hypnotic state during word presentation was not controlled for and effects may have come about due to inadequate anesthesia. Another difference between studies is the number of word repetitions, which was lower in the present study (9 as opposed to 15). The mere exposure effect, however, tends to be strongest with few (up to 8) stimulus repetitions (Bornstein, 1989). It is therefore more likely that the controlled level of anesthesia, and not the number of stimulus repetitions, explains our null findings.

In line with the preference ratings, word stem completion performance was comparable for primed, unprimed and distractor words. Because memory is generally stronger for emotional information, these observations corroborate the notion that affective stimuli were not processed by our patients and suggest that information processing during adequate anesthesia is not enhanced when emotions are involved. In a comparable number of patients, however, an implicit memory effect was recently found for emotionally negative information presented during general anesthesia maintained with isoflurane and nitrous oxide (Gidron, Barak, Henik, Gurman & Stiener, 2002). Although the effect was weak ($p < 0.05$, one-tailed) and hypnotic state during stimulus presentation not controlled for, this study suggests that information is processed more readily when negative emotions are involved. This could also explain why a memory effect was previously found in trauma patients during adequate levels of hypnosis (Lubke et al., 1999) but not in elective surgical patients, assuming that trauma surgery entails a more negative experience. Our null findings for emotional information processing may thus be confined to positive stimuli and do not preclude the possibility that emotionally negative stimuli are processed.

If one shifts the attention towards the non-emotional part of our investigation, a striking difference between unprimed words and chance performance appears in the word stem completion task. Taking only unprimed words presented at BIS 40 to 60 into consideration, patients generated fewer correct responses when words had been presented than when they had not. Brown and colleagues reported a similar unusual outcome for homophones and category exemplars presented during N_2O/isoflurane anesthesia (Brown, Best, Mitchell & Haggard, 1992), and explained their findings in terms of aversive conditioning: surgery being an intrinsically negative stimulus which becomes associated with the information presented during anesthesia may result in conditioned suppression of that information. If such response suppression occurred, it was not for primed words. The positive sounds may have opposed an aversive effect of surgery and neutralized response suppression. This would imply that affective sounds were processed by our patients after all. On the other hand, the effect may also have occurred due to chance. The notion of surgery as a negative reinforcer of information presented during anesthesia is at odds with most observations in this field of research. Usually memory is either absent or revealed through response facilitation, which contradicts the notion of aversive conditioning by surgery.

Some additional support for the notion that processing did occur comes from the blood pressure recordings. Pleasant stimuli typically induce an inhibition of the sympatic nervous system in addition to other distinct psychophysiologcal responses (Öhman, 1999). Similarly, we observed lower blood pressure in the priming condition than in the no-prime condition for both the nonsense and real word sets. This physiological difference between conditions, small though significant, may suggest that positive sounds were processed indeed. Unlike what would be expected from sympatic inhibition, however, lowered heart rate was not observed in the priming condition. Furthermore, a relation between blood pressure and subsequent affect ratings was observed for both primed and unprimed nonsense words. Although effects were stronger for the former, this similarity between conditions undermines the notion that physiological effects might discriminate between emotional and non-emotional information processing. The relation is nonetheless interesting for it suggests an effect of intraoperative physiological arousal on postoperative feelings toward relevant stimuli.

In summary, we conclude that no evidence of emotional information processing and affect modulation was found during propofol anesthesia titrated to BIS 40 to 60. This indicates that patients are not necessarily emotionally vulnerable or susceptible to therapeutic suggestion at this level. Some evidence of non-emotional information processing was found in the form of possibly suppressed responding with words presented during anesthesia, but this outcome is hard to explain within a larger theoretical framework.

6

Memory and affective priming during deep sedation with propofol and alfentanil

Introduction

The previous study (chapter 5) addressed memory and affective priming during adequate hypnotic state, as monitored by BIS values between 40 and 60. While information processing is rarely observed at this level, patients possibly evidenced memory in the form of suppressed responding with words presented during anesthesia. Unlike we anticipated, emotional stimulus processing could not be demonstrated as preferences for previously presented words nor was memory performance enhanced by the presentation of an emotionally positive sound that was linked to some of the words. Although laboratory studies have indicated that simple yet potent affective stimuli can be processed in the absence of conscious stimulus awareness (LeDoux, 1998; Murphy, Monahan & Zajonc, 1995; Murphy & Zajonc, 1993; Zajonc, 1980), studies of fear conditioning during anesthesia suggest that emotional learning and stimulus perception is easily attenuated by deepening hypnosis and is not preserved during general anesthesia (Dutton et al., 2002; Ghoneim, Block & Fowles, 1992). This may explain why affective priming could not be demonstrated in the previous experiment.

The present study therefore investigated affective priming during propofol and alfentanil anesthesia titrated to BIS 60 to 70, generally referred to as deep sedation. As in our previous study, a series of nonsense words was presented in combination with an affectively positive sound, and a different series of nonsense words was just repeatedly presented to patients during anesthesia. This within-subjects factor of affective priming served to separate reinforced from unreinforced emotional reactions to presented words (see chapter 5). The experiment was also an attempt to replicate the second study (chapter 3) which addressed memory function during deep sedation and individual differences therein. Again, we presented all patients with a series of relatively familiar Dutch words during anesthesia and tested them for memory, using the process dissociation procedure (PDP). PDP requires each subject to perform under two distinct conditions, i.e., an inclusion and exclusion test part, which both refer to presented and nonpresented words. In order not to loose too much statistical power, the 24 words used in this part of the investigation were not exposed to affective priming. This would have added another within-subjects factor beside manipulations of word type (target/distractor) and test condition (inclusion/exclusion), and would have yielded only a few critical items per measurement condition. Affective priming thus pertained to nonsense words only. As in study 2 (chapter 3), the isolated forearm technique supported BIS-monitoring of hypnotic state and enabled evaluation of patient wakefulness at regular intervals during anesthesia. In addition, patients were tested preoperatively on speed of information processing and memory function, but unlike study 2, tests also included an auditory memory task and an auditory perception task.

Materials and Methods

Following approval from the local human investigations committee, we invited healthy (ASA I-II) outpatients, scheduled for elective orthopedic surgery under general anesthesia at the ambulatory surgical unit of our institution, to be enrolled in our study. Patients gave written informed consent, were aged between 18 and 65 years, fluent in Dutch, and reported intact hearing and no history of drug abuse or current use of psychoactive medication.

Preoperative assessments

To address individual differences in memory function during anesthesia, we administered patients a series of tasks several weeks prior to surgery. As before (chapter 3), patients completed a visual word stem completion task and a computerized reaction-time task in order to assess their memory function and speed of information processing. The test session started with a 1-min study phase of 10 printed words that patients were instructed to pay attention to and memorize. Unlike in study 2, all patients studied the same list that comprised a mixture of words from lists A and B (see chapter 3). This new strategy eliminated variation in performance due to list differences that we observed and had to control for statistically in study 2 . Base rate completion for the 10 selected words averaged 0.26 (range, 0.07 – 0.46) in study 2 whereas mean hit rate equaled 0.70 (range 0.43 – 0.89) after a brief study period. Patients then completed the reaction time task, which required them to indicate the orientation of an arrow appearing on the computer screen (see chapter 3). Approximately 5 min after study, patients were shown 10 printed word stems that corresponded to the initial list. They were instructed to complete stems with study words or to use the first word coming to mind in case recall failed. After completing all stems, patients pointed out the words they remembered. For each individual we derived the number of study words used for stem completion (cued recall), the number of study words correctly recognized (recognition), and the mean reaction time after removing errors and outliers in the choice reaction task (reaction time 3 SD below or above three standard deviations of the mean).

Preoperative assessments also included tasks on auditory memory and auditory perception. Although we had found evidence (chapter 3) that preoperative memory function, tested in a visual modality is predictive of individual differences in memory function during anesthesia, a stronger relation could perhaps be found if pretest stimulus modality resembled posttest modality and nature of stimulus presentation during anesthesia. Priming effects, for instance, are generally weaker across sensory modalities than within modalities (Richardson-Klavehn & Gardiner, 1996). The auditory memory test included 10 words that had been used in a previous experiment and from which an average base rate completion could be derived (0.26, range 0.14 – 0.30). Word were presented one by one *via* closed headphones during 75 s. The computer program presented a different random order to each patient and repeated each word once with. Patients were instructed to pay close attention and to memorize all words. An auditory perception task (described below) subsequently served to divert attention. Approximately 5 min after study, patients completed an auditory word stem completion task. They were randomly presented with 10 stems corresponding to the words presented earlier and instructed to use stems as cues to recall these words. For each completion, patients indicated whether they remembered having heard that particular word during study. Next, we noted the number of correct stem completions (auditory cued recall) and correctly recognized words (auditory recognition) for each individual.

We also explored whether an individual's capacity to register auditory inputs in immediate sensory (echoic) memory would relate to variation in memory for words presented auditorily during anesthesia. While the early storage of visual information is known to last only a few milliseconds, physiological studies have indicated a much longer (10 s) time course for echoic traces (Samms, Hari, Rif & Knuutila, 1993). Our auditory perception test therefore contained two series of auditory stimuli that both lasted approximately 10 s. Stimuli were consecutively presented in the first series, whereas a second series contained parallel stimuli. The first series started with a 500 Hz tone and ended with a 300 Hz (i.e., lower) tone. In between, four letters (G, H, J, Q) and four numbers (3, 7, 5, 8) were played one after the other (in this order). Stimuli were digitally recorded in a male voice (first two letters, numbers) and female voice (last two letters, numbers) using a Macintosh Powerbook 3400 and SoundEdit software. They were played *via* closed headphones and patients reported afterwards what had been said by the man, by the woman, and whether the last tone was higher or lower than the first (in this order). Correct answers denoted a hit and a serial-perception score of 0 to 9 hits could thus be obtained. The second series also started and ended with a tone (400 Hz vs. 500 Hz), and in between four sentences of 5 s each were presented two by two (dichotically). Sentences had been recorded in a female voice and contained general knowledge information (Queen *Beatrix* came to the throne in 1980; The *earth*'s circumference approximates 40,000 km; The average life expectancy is higher for *women*; Mixing the *colors* blue and yellow yields green). After hearing this more complex series of stimuli, patients first reported on anything they had heard and information pertaining to any of the sentences was scored as a hit (score 0 to 4). They further indicated whether the end tone was higher or lower than the one at the start (score 0 or 1), and finally, they were given a cue for each sentence (indicated above in italic) to trigger the echoic trace. If cued responses conveyed more specific information than initially reported, it denoted a hit (score 0 to 4). Patients could thus obtain a parallel-perception score between 0 and 9 hits as well.

Anesthetic technique

Chapter 3 describes the protocol we adhered for induction and maintenance of anesthesia (no premedication, induction and maintenance with propofol, TCI, bolus alfentanil, succinylcholine and norcuron) and the registration of EEG (two-referential montage, electrode impedance < 5KΩ). The anesthesiologist titrated propofol plasma concentrations to BIS (version 3.2) values between 60 and 70 during which, before surgery commenced, patients were played a series of words *via* a laptop computer and closed headphones.

Stimulus material

To address both memory and affective priming, we presented three word series. The first series consisted of relatively familiar Dutch words for which memory effects had previously been found after presentation during deep sedation (chapter 3) and general anesthesia (chapter 5). We initially started out with 44 words but removed 20, so as to create a more reliable (i.e., consistent) set which was subsequently used in study 3 and the present study. Patients were played two lists of six words during anesthesia (12 targets) and were tested on four lists, thus including two that had not been presented (12 distractors). A counterbalanced design assured that words appeared both as a target and as a distractor in the total study sample. Targets were presented 10 × consecutively with a 3-s delay in between repetitions and presentation of the first series lasted 8 min.

The second and third series each contained six nonsense words and were adopted from chapter 5. In that particular study, three lists of nonsense words had been created to investigate the effect of mere (unreinforced) repeated exposure *versus* affective (reinforced) priming on preference for presented words, compared with words that had not been presented. Similarly, we played patients one list (the second series) without affective prime (mere exposure condition) in the same way we presented the familiar Dutch words. The third series of words, by contrast, were presented in combination with a positive sound (affective prime, see chapter 6) tuned to the individual's preference. The 4-s sound preceded each word presented in this series, and as in the first and second series, each target was played 10 × before a new one followed. In total, presentation of the second and third series took 4 and 5 min, respectively. An overview of the study design is shown in Figure 1.

Awareness

Although deep sedation as monitored by BIS clearly induces unconsciousness (chapters 3 and 4), we again included a behavioral measure of wakefulness and assessed response to command at regular intervals during word presentation. We substantially reduced the number of commands, however, because responsiveness per se had little predictive value for variation in postoperative memory performance (chapter 3). Instead of assessing responsiveness each time a new target word was to be presented, we administered commands in between word series (2 commands), once prior to, and once after word presentation (2 commands) and once during the first series (1 command). As such, patient awareness was assessed once every six target words. Neuromuscular blocking drugs necessitated the use of the isolated forearm technique (IFT) which prevented one hand from being paralyzed, allowing it be moved to indicate awareness spontaneously or upon request. We asked patients for conditional responses as to establish awareness unequivocally (see chapter 3). After all words had been played and before patients entered the operating room, the anesthetic was increased to BIS ≈ 45, and electrodes, headphones and IFT cuff were removed.

	Familiar Dutch words (n = 24)				Nonsense words (n = 18)		
	List 1	List 2	List 3	List 4	List 5	List 6	List 7
group A	TI	DI	TE	DE	Tp	Tnp	D
group B	DE	TI	DI	TE	D	Tp	Tnp
group C	TE	DE	TI	DI	Tnp	D	Tp
group D	DI	TE	DE	TI	Tp	Tnp	D

Figure 1. Study design. Patients were randomly assigned to one of four groups (A to D) and were all presented with four word lists during anesthesia (targets; T). Two of the lists contained relatively familiar Dutch words for which memory was tested under inclusion instructions (TI) or exclusion instructions (TE). Two other lists contained nonsense words that were either presented in combination with a positive sound (Tp) or were just merely repeated (Tnp). Patients were tested on all lists, thus including the three that had not been presented during anesthesia (distractors; DI, DE, D).

Testing

All patients were interviewed and tested in the recovery ward within hours after surgery and shortly before hospital discharge. Four questions addressed conscious recall of perioperative events ("What is the last thing you remember before falling asleep?", "What is the first thing you remember after waking up?", "Do you remember anything in between?", and "Did you dream?"). We then administered the word stem completion task in combination with PDP, using the same computer and headphones as before. The test consisted of an inclusion and exclusion part, the order of which randomly varied between patients. Both parts included stems corresponding to words from one target and one distractor list. The inclusion part required patients to complete stems with the corresponding words presented during anesthesia or to use the first word coming to mind in case recall failed. The exclusion part required patients *not* to use presented words for stem completion. In both parts, patients were correctly informed that some stems could be completed to words presented during anesthesia while others could not. A computer program generated a random order of 12 word stems for each patient in each test condition and the observer entered responses into the computer. Patients were instructed to report each word they thought to have heard during anesthesia (cued recall test).

Patients subsequently rated the nonsense words for evoked pleasure on a 6-point Likert scale as used previously (chapter 5) with a smiling, happy figure to the right indicating 'very much', and a frowning, unhappy figure to the left indicating 'not at all'. This test included nonsense words presented during anesthesia with or without affective prime in addition to 6 distractor words. The computer program generated a random order of 18 words and presented each on the computer screen and twice auditorily, with a 1-s interval in between repetitions. After seeing and hearing the word, patients indicated to what extent it evoked a pleasant feeling and they were encouraged to respond spontaneously. The observer entered ratings into the computer as a score between 6 (very much) and 1 (not at all).

Finally, patients were shown all target and distractor words used in this study. One list contained the familiar Dutch word set and another the nonsense word set. For each word, patients decided whether or not it had been played to them during anesthesia. They were correctly informed that both lists contained a number of presented words.

Statistical analysis

The first part of data-analysis pertained to the issue and nature of preserved memory function and included data obtained in the postoperative word stem completion task. Stem completion to one of the 24 study words was scored a “hit” and the hit rate for targets was compared to the distractor hit rate (chance performance) in both the inclusion and exclusion conditions, using paired-samples t-tests. Absence of memory would be indicated by chance performance in both parts of the test, whereas an implicit memory effect would be evident if hit rates for targets exceeded those for distractors in both test conditions. An explicit memory effect, by contrast, would be reflected by higher target hit rates in the inclusion condition as opposed to lower hit rates in exclusion condition. Such a difference between test conditions would suggest response control, which may be observed in the absence of conscious recall (i.e., unconscious controlled memory) or in its presence (see chapter 3).

A second part addressed individual differences in memory function during anesthesia by relating patient hit scores for targets in the inclusion condition of the postoperative word stem completion test (outcome variable) to scores obtained in the various preoperative tests (predictor variables). We first examined correlations between outcome and predictor variables and, taking sample size considerations into account, performed regression analysis (see also chapter 3).

In a third part, we analyzed obtained ratings for nonsense words to elucidate affective priming effects during anesthesia. Higher ratings were expected for primed targets than for unprimed targets due to affective priming of the former. Because repeated exposure may by itself induce positive affect toward stimuli (i.e., mere exposure effect), ratings for unprimed targets were expected to be higher than for distractors. Differences in mean ratings were analyzed with a General Linear Model for repeated measurements. $P < 0.05$ was considered statistically significant and data are presented as mean ± SD.

Results

Eight patients could not be included either for various reasons, i.e., because their operation was postponed or cancelled (n = 3), because they withdrew from the study on the day of surgery (n = 3), or because their scheduled surgery time was too short to allow an extra period of anesthesia (n = 2). Another two patients were excluded after being enrolled, one whose word presentation at the target BIS level could not be accomplished, and one who had been given midazolam to relieve an epileptic insult that occurred during anesthesia. As midazolam typically induces anterograde amnesia, the memory test results for this patient were considered invalid.

Included patients (12 men, 18 women) were 35 ± 12 yr of age and remained anesthetized for 40 ± 5 min in the presurgical study period followed by 41 ± 13 min for surgery. BIS was somewhat lower during presentation of the first word series (61.8 ± 4.5) than during the second (63.8 ± 3.7) and third series (63.0 ± 5.8). In the first series 77% of words was presented within the BIS target range, compared with 90% and 82% in the second and third series. The IFT was implemented during 25 ± 3 min and 144 commands were given overall (5 ± 1 per patient). Eighteen patients (60%) responded unequivocally at some point during their anesthetic (range 1 – 5 times) whereas the remaining did not respond to command at any time. Overall, no response was observed to 104 commands (72%), equivocal response to 3 commands (2%) and unequivocal response to 37 commands (26%). Testing took place 3.6 ± 0.5 h after word presentation and 2.9 ± 0.5 h after recovery from anesthesia.

Memory Function

None of the patients remembered any of the words presented in the first, second or third series during anesthesia. Two patients (7%) reported conscious recall of verbal commands and both had responded unequivocally to three commands. The average BIS seemed slightly elevated in one of these responding patients (66.1) but not in the other (62.6). Presentation of word stems (cued recall) resulted in 5 correct recollections versus 21 incorrect recollections overall. When memory was prompted even further by showing target words mixed with distractors (recognition test), patients did not recognize more words correctly than incorrectly. The two who had displayed conscious recall of commands did not perform better than average on these measures of memory. In general, observations indicated absence of unprompted and prompted recall for presented words.

Observed hit frequencies for targets and distractors in both parts of the word stem completion test are shown in Table 1. Presentation of words during anesthesia did not promote stem completion to study words in the inclusion condition, nor were patients able to exclude presented words. Although the target hit rate in the exclusion condition was somewhat lower than that in the inclusion condition, the two did not differ significantly ($p = 0.2$). Patients thus showed no evidence of implicit memory or response control, and further inspection of the data revealed that conscious recall made no difference in this respect.

Table 1. Hit frequencies (hit rate ± SD) in the two conditions of the postoperative word stem completion test.

List	Inclusion Condition	Exclusion Condition
Target	52 (0.29 ± 0.21)	41 (0.23 ± 0.17)
Distractor	52 (0.29 ± 0.19)	50 (0.28 ± 0.19)

Individual Differences

Preoperative data were obtained in twenty of the included patients. Observed correlations between preoperative measures and the number of target hits in the inclusion condition of the postoperative word stem completion test are shown in Table 2. The limited sample size did not allow for an extended regression analysis and data were therefore merely explored. Of the various preoperative indices, the numbers of hits in the auditory memory test (standardized $\beta = 0.44$, $p < 0.05$) and serial perception task ($\beta = -0.59$, $p < 0.01$) together explained most (41%) of the variance in hit scores for words presented during anesthesia.

Table 2. Correlation between preoperative measures and postoperative target hit scores in the inclusion condition of word stem completion test.

Measure	Mean ± SD	Pearson correlation	p-value
visual Cued Recall	8.5 ± 1.3	0.29	0.22
visual Recognition	6.8 ± 2.0	0.22	0.34
auditory Cued Recall	6.6 ± 1.5	0.28	0.23
auditory Recognition	5.1 ± 1.7	- 0.18	0.45
Reaction time	404 ± 67	0.08	0.75
serial Auditory Perception	5.2 ± 2.0	- 0.49	0.03
parallel Auditory Perception	2.7 ± 0.9	0.12	0.86

Affective Priming

As in the previous study (chapter 5), the giggling sound of a baby most often served as the affective prime (n = 18; 13 female, 5 male), followed by a piece of classical music (n = 9; 3F, 6M) and a baseball game stadium roar (n = 3; 2F, 1M). Affect ratings for primed nonsense words (3.59 ± 0.72) or words repeatedly presented (3.42 ± 0.69) did not significantly differ from the average rating for distractors (3.47 ± 0.77) (p = 0.5).

Discussion

This study failed to demonstrate evidence of memory or affective priming during deep sedation induced and maintained with propofol. Memory performance was at chance level and preferences for words presented in combination with a pleasant sound were only slightly enhanced. These results confirm our previous observations (chapter 5) and suggest that emotional stimuli are not necessarily processed more readily during anesthesia than non-emotional information. Affect modulation could again not be demonstrated despite the apparent reduction in depth of hypnosis during stimulus presentation that we accomplished in the present study. These results raise questions on the prerequisites for "nonconscious affect", which is otherwise so robustly observed in laboratory studies of emotion with wakeful subjects. These studies suggest that conscious awareness is not a necessary condition for the induction of affect, but this does not warrant the conclusion that emotional learning and responses are easily induced during anesthesia. Our studies and those of others (Dutton et al., 2002; Ghoneim et al., 1992) indicate that when consciousness in lowered pharmacologically rather than experimentally, processing of emotional stimuli is readily affected and quite quickly abolished, as compared with processing of non-emotional stimuli. Although we found no evidence of either type of process in this study, the conclusion is that affect modulation during anesthesia is far more controversial than standard, non-emotional priming of specific information. Our findings are in line with the limited body of evidence for processing of emotional information during anesthesia (Merikle & Daneman, 1996).

Memory function could not be demonstrated either, which merits further mentioning in two respects. First, the average BIS during word presentation was significantly lower, compared with our previous study during deep sedation (chapter 3) in which patients did show evidence of weak explicit memory function. The two BIS readings differed very little (61.8 vs. 64.0) but possibly enough to alter memory phenomenology. Where subjects were previously able to employ presented information in the two conditions of the word stem completion test, patients in the current experiment demonstrated no response control or evidence of implicit memory function. They again seemed better at excluding target words rather than at including them but this time not significantly so. Secondly, we observed substantially less conscious recall in addition to absence of response control, which is a finding that converges with the notion put forward in chapter 3, that weak explicit memory function (i.e., response control) is associated with conscious recollection of intra-anesthetic events. When explicit memory function is lost, so is conscious recall. This does not imply, however, that patients were unconscious throughout the anesthetic procedure, because we again unequivocally established wakefulness in a substantial number of cases. Our data emphasize that patients may perceive and process considerable pieces of information, such as verbal commands, without acquiring and retaining a conscious memory trace. Apparently, as in real life, information processing per se is not sufficient for such learning and memory to occur.

The reduced incidence of conscious recall may in part be explained by the lower BIS level we accomplished overall in the present study, as compared with our previous study (chapter 3). Another reason may be found in the reduced number of commands which may have aroused patients less intensely and/or less frequently.

Individual differences in memory performance could not be addressed satisfactorily due to the limited number of patients that we were able to include, and to test preoperatively in particular. It is worth mentioning, however, that the observed correlations resembled those observed previously (chapter 3) that drew on the relation between postoperative hit scores and preoperative visual memory test performance. This replication, in the absence of statistical significance, tentatively supports our claim that variation in memory function during anesthesia may be related to rather stable patient characteristics (chapter 3). It should further be noted that the present findings suggest a potentially important role for auditory indices, some of which predicted a considerable proportion of variation in postoperative test performance, especially when taken into consideration jointly. In this respect, we identified preoperative cued recall as a reasonably strong predictor of performance, which confirmed our previous findings (chapter 3). In addition, the impact of short-term sensory processing was identified. The inverse relation to postoperative memory test performance, however, was contrary to what we anticipated and is certainly difficult to explain. It might indicate that patients who readily perceive (auditory) stimuli are more susceptible to the pharmacological effect of hypnotic agents and the registered amounts of propofol infusion provide some support for this speculative line of reasoning. As we aimed to identify patients at risk, the clinical value of this predictor variable is questionable.

7

General discussion

This thesis was designed to investigate memory function during anesthesia. Such an investigation may cross-validate prevailing theories of human cognitive functioning, in particular those that implicate absence of conscious awareness, and bears on patient management during routine surgical procedures that require general anesthesia. All experiments relied on a priming paradigm adopted from behavioral studies of memory, perception and attention, which have demonstrated that human information processing continues without apparent stimulus awareness or recollection. The controversy over what establishes conscious or unconscious information processing (reviewed in chapter 1) was addressed twofold: EEG bispectral index (BIS) served to monitor patients' hypnotic state during auditory stimulus presentation, and close attention was paid to the memory test material and procedure as to infer the nature of stimulus processing underlying task performance. Studies aimed to elucidate the relation between hypnotic adequacy and memory function for two types of information and general findings, as well as limitations of presented studies and implications for future research are discussed below.

Memory function and hypnotic adequacy

While many experiments have addressed preserved information processing during anesthesia, few controlled for level of hypnosis during stimulus presentation. This major flaw in research methodology may to a large extent be attributed to problems surrounding measurement of anesthesic depth and lack of reliable indicators thereof. Clinical parameters that were recently developed, however, enable more sophisticated explorations of cognitive plasticity under anesthesia. The first strong evidence of a relation between memory for words presented during anesthesia and depth of hypnotic state, as measured by BIS, was recently found after examining a large sample of trauma patients (Lubke, Kerssens, Phaf & Sebel, 1999) in whom depth of hypnosis varied widely as the severity of injury imposed restrictions on the amount of anesthesia that could be administered. This thesis, by contrast, investigated memory function in relatively healthy elective surgical patients in whom different levels of hypnotic state were distinguished by studying them either during surgery under general anesthesia (chapters 2 and 5) or shortly prior to surgery during deep sedation (chapters 3, 4, and 6). Patients were repeatedly exposed to a series of words in each study and tested for memory foremost with direct measures (conscious recall, cued recall, recognition). Based on previous work (Lubke et al., 1999; Lubke, Kerssens, Gershon & Sebel, 2000), memory function was expected stronger during deep sedation.

A first conclusion that can be drawn from this thesis is that presented work supports the hypothesis asserting dependency of memory function on hypnotic state. The main findings include an effect of word presentation during deep sedation at an average BIS of 64 (chapter 3) whereas such an effect could be not demonstrated for words presented at deeper planes of hypnosis (chapters 2, 5 and 6). In chapter 3, memory was revealed through an ability of patients to correctly include and exclude presented words in the post-operative word stem completion test. This finding of response control, in the absence of conscious recall, established evidence of weak explicit memory function. Such evidence has previously been found in patients undergoing emergency cesarean section (Lubke et al., 2000) and has been reported by others as well (Stapleton & Andrade, 2000). Taking the cesarean section study into account, in which the average BIS during word presentation was substantially higher (± 76), comparison of test performance further supports dependency of memory function on hypnotic state. Where the sectio patients included and excluded presented words significantly better than nonpresented words, response control in chapter 3 seemed weaker and did not support distinctions between target and distractor words in the inclusion and exclusion test conditions. Patients just managed to follow instructions and were merely capable of selecting *for* or *against* presented words. Despite its weakness, response control was reliably observed and as such, this thesis found evidence of explicit memory function only.

These first conclusions need further refinement, however, and seem to ignore one particular finding reported in chapter 5. Although patients in that study were overall not inclined to complete stems more often to words presented during general anesthesia, post hoc analysis of data suggested an effect of word presentation after all. Without giving them exclusion instructions, patients responded less often with target words played at BIS values between 40 and 60 and apparently suppressed material pertaining to the intraoperative period. One tentative explanation for this unusual finding draws on the hypothesis that surgery entails an aversive event that is rather forgotten than remembered (Brown, Best, Mitchel & Haggard, 1992). Stimulus material presented contiguously with surgery would acquire a similar negative quality and therefore be used less frequently upon memory testing than material that was not intraoperatively presented. Suppression of unwanted memories is controversial in general, but recently gained renewed interest and support after neurobiological and behavioral research into the phenomenon (Anderson & Green, 2001). In studies during anesthesia, however, memory effects are generally manifest in enhanced responding with intraoperatively presented stimuli (Merikle & Daneman, 1996), which contradicts the notion of aversive conditioning through surgery. Even patients who undergo very "dramatic" life-threatening procedures, such as trauma or cardiac surgery, display traditional memory priming effects. Furthermore, no evidence of response suppression was found in the other studies described in this thesis, which casts further doubt on the interpretation of response suppression in terms of aversive memory. All in all, the post hoc finding reported in chapter 5 is controversial and does not provide clear evidence of memory function during general anesthesia.

Chapter 2 on the other hand suggests that memory function is abolished when controlled, adequate hypnosis is provided. A priming effect that was previously induced by word stimuli (category exemplars) in studies that did not specifically address the level of hypnosis during stimulus presentation (Jelicic, Bonke, Wolters & Phaf, 1992; Roorda-Hrdlicková, Wolters, Bonke & Phaf, 1990), could not be replicated under controlled circumstances. This finding is supported by another study in which the effect of BIS monitoring versus traditional (autonomic nervous system) monitoring on memory for a story played during anesthesia was compared (Struys et al., 1998), but contradicts the evidence of preserved memory function in trauma patients during adequate levels of hypnotic state (Lubke et al., 1999). An explanation for the discrepancy may be found in the variation in depth of hypnosis that was observed within and between patients undergoing trauma surgery. This variance does not preclude the possibility that temporary and inadvertent lightening of hypnotic state affected memory for words presented during apparent adequate hypnosis. Such fluctuations by contrast did not arise in our study (chapter 2) and the study by Struys and colleagues (1998), which strongly suggests that a controlled level of adequate hypnosis supports suppression of memory function. To further address this issue, a new study was recently devised using the same word stimuli that trauma patients had been presented with, but this time, depth of anesthesia (maintained with propofol or isoflurane and supplemented with alfentanil) was titrated to BIS 50 during stimulus presentation. Preliminary data of 64 elective surgical patients (mean BIS ± SD during word presentation = 49.3 ± 5.5) confirm the results obtained in chapter 2 and failed to replicate the memory effect previously observed in trauma patients (Ouchi, Sebel & Kerssens, 2002, see Appendix A). PDP results further indicate absence of either implicit or explicit memory functioning. It is therefore concluded that memory function is highly unlikely during controlled levels of adequate hypnosis monitored with modern EEG-derived indices such as BIS, acknowledging that many demonstrations of memory for specific information presented during anesthesia may hitherto have come about due to moments of inadequate anesthesia.

The exceptional brain

Although this thesis indicates that memory function in elective surgical patients declines as depth of sedation increases and is not observed during general anesthesia, it has also become clear that variation between individual patients exists. Such differences are easily concealed when the investigator relies on group mean measures of performance and have generally been neglected as a potentially reliable and important source of information (Millar, 1993). Conversely, little is known about individual variation in memory function during anesthesia and the factors contributing to it. A role for personality characteristics such as extraversion, neuroticism, susceptibility to mental (as opposed to pharmacologically induced) hypnosis and trait-anxiety have been proposed (Ghoneim & Block, 1992; Millar, 1993) but apart from an occcasional study (Donker, Phaf, Porcelijn & Bonke, 1996), systematic explorations are lacking.

When individual differences that were observed in chapter 3 are taken into account, the prevalence of preserved explicit memory function during deep sedation needs further refinement. Group means reported in chapter 3 initially indicated that patients in general controlled their responses to word stems corresponding to words presented during anesthesia. Further exploration of the data, however, revealed that the overall effect was to be attributed to a particular subset of patients, i.e., to those with conscious recall of the commands they had been given whilst being deeply sedated. The number of commands was comparable for the two groups, as was the depth of hypnosis (BIS ± 67) when patients had responded unequivocally. Under similar circumstances, however, patients who developed conscious recall were found more responsive. This difference could unfortunately not be traced to any (patient) characteristic or variable in particular but the impact was quite clear: increased wakefulness contributed to conscious recall and (explicit) memory function. Apart from the fact that this finding confirms the notion that memory function depends on hypnotic (in)adequacy as measured by response to command, for clinical purposes it is important to recognize that the larger group (84%) of patients displayed no evidence of memory function during deep sedation induced and maintained with propofol.

Although we established an apparent relation between the degree in which patients responded to command and subsequent memory for the event (chapter 3), the relation was far from perfect, and as such, dependency of memory function on hypnotic (in)adequacy was not satisfactorily addressed in this thesis. About 50% of patients responded to command during deep sedation anesthesia without developing conscious recall (chapters 3 and 6) and a cutoff score for responsiveness appears no more predictive. In the first study of deep sedation (chapter 3), for instance, patients with conscious recall responded unequivocally to 30% of commands on average. This response rate would identify eleven patients in the second study (chapter 6) as being at risk of memory function, whereas only two developed conscious recall, one of whom displayed evidence of response control in the word stem completion task. The discrepancy between responsiveness and manifestations of memory emphasizes a necessity to further investigate individual differences. While a substantial number of deeply sedated patients may respond to provoking events such as a verbal command, only few develop memory. It is these patients that we would want to identify in particular.

Based on personal hunches and scarce relevant literature on individual variation in learning and memory (e.g., Ackerman, Kyllonen & Roberts, 1999), it was attempted to pin down sources of variation in intra-anesthetic memory function. Online parameters of brain activity (chapter 4) were particularly good at monitoring wakefulness but failed to discriminate between patients with and without conscious recall, a finding that underlines the clinical usefulness of parameters such as BIS to monitor depth of hypnosis but not necessarily memory function. A more promising venue of research may be found in rather stable patient characteristics and the studies presented here (chapters 3 and 6) suggest that specific cognitive factors, such as a patient's ability to retain information in general, relate to memory function during anesthesia. The predictive value of this particular factor (preoperative memory performance) is not necessarily questionable after it failed to gain statistical significance in chapter 6: Preliminary data of yet another study (Ouchi et al., 2002) revealed a similar (0.29) and significant ($p < 0.05$) correlation between preoperative and postoperative memory task performance, and thus confirmed the results reported in chapter 3. It must be recognized, however, that its clinical value is limited as differences in preoperative scores explained a relatively small proportion (10%) of variance in word stem completion to words presented during anesthesia, and failed to distinguish between patients with and without conscious recall. More research into other (cognitive) domains is needed to identify the pathways of exceptional brains and a potentially important domain pertains to processes involved in auditory perception (chapter 6). From a methodological point of view, investigators are encouraged to include at least 40 patients in their studies of (single) predictor variables: as memory effects for material presented during anesthesia are generally small, the statistical rule of thumb to study 10 subjects per variable seems insufficient in this particular field of research.

Beside differences between patients that were accidentally observed or specifically addressed, a few other salient variables merit further mentioning and attention when it comes to elucidating variation within and between studies. These include the arousal or stress level of patients undergoing surgery, the duration of anesthesia and sex differences. It was previously pointed out that trauma patients possibly displayed evidence of memory function during adequate levels of hypnosis due to residual effects of lightened anesthesia. Another reason, however, may be found in the stressful situation patients generally found themselves in and the memory enhancing effect of stress hormones (Cahill & McGaugh, 1996; McGaugh & Cahill, 1997). In addition, these patients had been given epinephrine (adrenaline) –a stress hormone with renowned memory modulatory effects (Cahill & McGaugh, 1996)– on a regular basis to meet their medical requirements. It is not unlikely that the situation and drugs increased the probability of memory function in trauma patients. chapter 2 further reported that lengthy operations were associated with better memory performance, a post hoc finding that may bear upon the conditions of memory storage and the disruptive effect of retroactive interference in particular. This type of interference refers to the notion that events happening after the to-be-remembered (critical) event can create forgetting of the critical event. Prolonged anesthesia in this case possibly enhances storage of information as relatively few other items enter the system after critical information has been presented. When the patient, by contrast, awakens shortly after stimulus presentation, a host of (novel) stimuli impinge on the subject and may disrupt storage and consolidation of presented information. This tentative explanation of findings reported in chapter 2 suggests that patients undergoing extended surgery are more at risk of developing memory for intraoperative events, especially under tranquil circumstances (e.g., stable noxious stimulation, a serene operating theater). A third source of variation pertains to sex-related differences in pharmacokinetics and pharmacodynamics (Ciconne & Holdcroft, 1999). While the studies presented in this thesis included both male and female subjects and never yielded statistically significant differences between the sexes, my personal observation is that men tend to outperform women on tasks assessing memory for material presented during anesthesia. Such latent differences, if they exist, are difficult to explain in terms of memory function but rather could arise from sex-dependent effects on drug metabolism. The significance of this particular observation is not to be exaggerated (although it interesting it note that the sample of trauma patients in whom memory function was demonstrated consisted largely of men, and that the subsample of male patients undergoing urologic surgery performed particularly well in the study reported in chapter 2), yet investigators may take sex differences into consideration when designing studies and analyze the results.

Clinical Outline

It is becoming increasingly clear that memory function and perception during anesthesia is best regarded as a continuum rather than an all-or-none phenomenon. This notion is already found in prevailing conceptions of memory function during anesthesia (e.g., Bailey & Jones, 1997; Jones, 1989; Schwender et al., 1997) which heavily relied on dissociations between indirect and direct measures of memory in their attempt to elucidate the nature of residual memory function. Modern approaches, by contrast, make minimal assumptions about memory tasks and tend to monitor brain activity or patient responsiveness during critical events. As a result, stages of memory function are empirically rather than hypothetically discerned and are likely to bear more strongly on clinical phenomena and practice. Because studies drawing on a modern approach are limited in number, a preliminary model of memory function in elective surgical patients is extrapolated from the results reported in this thesis and those obtained in relevant studies reviewed in chapter 1:

- **BIS 100 - 80** explicit memory function

  Although no study has yet addressed this level of hypnosis using the PDP, it is reasonable to assume that patients display response control (explicit memory function) as they do at deeper levels of sedation (Lubke et al., 2000; this thesis). Low anesthetic concentrations rapidly attenuate conscious recall and patient responsiveness to mild stimulation. Conscious recall is unlikely (5%) at BIS values below 80 (Glass et al., 1997; Iselin-Chaves et al., 1998; Liu et al., 1997) whereas responsiveness is still observed in a substantial number of patients (> 50%, Iselin-Chaves et al., 1998; Kearse et al., 1998).

- **BIS 80 - 70** weak explicit memory function

  Patients may display response control in the absence of conscious recall (unconscious-controlled memory) for words presented at this level (Lubke et al., 2000). Patient responsiveness was not assessed in this study but may still be expected to occur in 50% of patients (Iselin-Chaves et al., 1998; Kearse et al., 1998). Because conscious recall rapidly deteriorates at low anesthetic concentrations, weak explicit memory function could already be observed in the lower range of the previous level (BIS 80 - 90).

- **BIS 70 - 60** weak explicit memory function (15%), or
  no memory function (85%)

  A minor proportion (15%) of patients may display response control for words presented at this level in the absence of word recall or recognition (this thesis). This subgroup of patients is likely to remember salient intra-anesthetic events, such as responding to verbal command (this thesis). Responsiveness is still observed in a substantial number of patients (60%, this thesis), most of whom (85%) will have no recollection of the event, and will not display response control nor evidence of implicit memory function on postoperative memory tests (this thesis).

- **BIS 60 - 40** no memory function

  A small proportion of patients (5%) may still respond to mild prodding or shaking at this level of hypnosis (Iselin-Chaves et al., 1998; Kearse et al., 1998) whereas response to verbal command is fully abolished (Flaishon et al., 1997; this thesis). Implicit memory function is possibly preserved under particular circumstances (e.g., psychophysiological stress, temporary inadequate hypnosis) but is otherwise highly unlikely (Ouchi, Sebel & Kerssens, 2002; Struys et al., 1998; this thesis).

In contrast to traditional models of memory function (Jones, 1989; Schwender et al., 1997), this model does not support a stage of implicit memory function (in old models referred to as "subconscious awareness with implicit recall") whereas it does acknowledge that perception may continue even during general, so-called adequate, anesthesia. There is as yet insufficient evidence to assume that perception is abolished below a certain threshold of hypnosis, even though common behavioral indices (e.g., responsiveness, memory test performance) suggest so. It would be very interesting to see how neurophysiological parameters of auditory information processing, such as the AER (Thornton & Sharpe, 1998; Van Hooff et al., 1995), behave during BIS monitoring of adequate hypnosis and cross-validation of EEG-monitoring techniques is already attempted (Struys et al., 2002).

This preliminary model is largely based on investigations using propofol anesthesia, but may just as well apply to other drug regimens. Based on the studies presented in this thesis, it is suggested that exceptional findings, such as a 5% incidence of conscious recall during adequate levels of hypnosis maintained with isoflurane (Glass et al., 1997), may reflect individual differences rather than common practice and investigators are encouraged to pay close attention to the distribution of their data. The overall picture outlined above rather indicates gross central nervous system suppression as BIS decreases below 70.

Affective Primacy

A second goal of this thesis was to address the affective primacy hypothesis (Zajonc, 1980) which asserts that emotional reactions can be evoked with minimal stimulus input and virtually no cognitive processing. Laboratory studies of wakeful subjects in whom stimulus awareness is attenuated experimentally to yield chance-level recognition, have confirmed the hypothesis time after time (Bornstein, 1989; Murphy, Monahan & Zajonc, 1995; Murphy & Zajonc, 1993) and have demonstrated that an emotionally relevant stimulus imposes a particularly strong effect on behavior when one is not aware of its presence or influence. Swift processing of potential threat (and conversely pleasure) presumably serves a biological function in many species including mankind (LeDoux, 1998) and subcortical structures in the brain have been identified to mediate such information processing (LeDoux, 1998, chap. 6; Morris, Öhman & Dolan, 1998). This particular field of research suggests that patients under anesthesia are emotionally vulnerable, especially when surgery implies exposure to pain, which may not be uncommon (Russell, 1993), or when threatening information is communicated by the medical staff present. Alternatively, the "problem" may be turned to an advantage by presenting therapeutic suggestions during the operation (Andrade, 1995). As the impact of such emotional stimuli is questionable (Merikle & Daneman, 1996), evidence for preserved, and primacy, of emotional information processing is lacking during anesthesia. Affective priming with semantically simple stimuli such as sounds, however, has never been attempted.

The two studies that investigated processing of emotionally positive sounds along with non-emotional information processing (chapters 5 and 6) failed to confirm the affective primacy hypothesis. Both reinforced and unreinforced preferences for otherwise emotionally bland word stimuli were not successfully evoked during anesthesia, whether patients were adequately anesthetized (chapter 5) or not (chapter 6). The difference in preference for affectively primed *versus* non-affectively primed words was somewhat larger in the latter study ($\Delta = 0.17$ as opposed to 0.03 in the former study) but neither type of word in either study was preferred over those not presented during anesthesia. Where similar experiments in the laboratory with a comparable number of subjects yielded robust effects of positive affective priming and mere exposure on preference ratings ($\Delta \approx 0.30$ compared to unprimed or new stimuli), our null findings suggest that (general) anesthesia rapidly attenuates emotional information processing and affect modulation. This notion is supported by studies of conditioned fear and skin conductance responses (Dutton et al., 2002; Ghoneim, Block & Fowles, 1992), and might be interpreted as an advantage from a clinical (patient vulnerability) point of view. Presented studies lend no support for the notion that emotional information must be treated specially during deep sedation or general anesthesia maintained with propofol. They confirm the controversy over intra-anesthetic promotion of positive affect, and cast doubt on the primacy of nonconscious affect.

Limitations of the present studies

Positive versus negative emotion

The present studies, as many others in this field of research, were confined to positive affect manipulations for obvious reasons. Although selected stimuli were equally effective as negative sounds in bringing about a strong feeling (Bradley & Lang, 1999), the use of strictly pleasant stimuli imposes a restriction on what may be inferred from the present studies. By no means do they imply that aversive information is likewise not processed during anesthesia and some indication of such processing was recently reported (Gidron, Barak, Henik, Gurman & Stiener, 2002). At a theoretical level, it is important to acknowledge that prevailing models of emotional learning (e.g., LeDoux, 1998) are largely based on a fear conditioning paradigm which evolves around aversion. Such models have provided invaluable insights into the mysterious underpinnings of emotional life –quoting LeDoux – but should not be mistaken for an all-encompassing theory of emotion. If we want to pursue emotional life during general anesthesia, the effect of mild aversive stimuli (such as a loud noise or mild electric shock that is used to establish return of muscular activity during surgery) may be investigated in volunteer studies, or an equally simple and potent conditioning paradigm may be developed for pleasant emotion.

Sounds versus pictures

Another restriction that this particular research setting imposes on the experimenter is that auditory stimuli are to be used. Affective priming studies in the laboratory, by contrast, rely on pictures to induce and reinforce an emotional reaction (preference) in participants. Although preferences may just as well be observed for auditory stimuli, pictures generally yield stronger effects (Bornstein, 1989). The affective priming paradigm that the present studies have employed could thus be suboptimal from an experimental point of view.

Attempted versus true replication

The affective priming employed in two of the presented studies was closely modeled after that used by Zajonc and colleagues (Murphy, Monahan & Zajonc, 1995; Murphy & Zajonc, 1993) but did not prove successful in terms of experimental effect. This could mean, as has been argued throughout this thesis, that emotional stimuli are not processed during deep sedation and general anesthesia. An alternative explanation for the present null findings, however, is that the paradigm was unsuccessfully replicated. For a start, sounds were used as an affective prime instead of pictures and their repeated presentation could also have promoted boredom rather than a genuine positive feeling. In addition, priming effects were assessed after several hours as opposed to (an estimated) several minutes in laboratory experiments. Given that mere exposure effects for target stimuli presented during anesthesia were not observed either, this lends support for the conclusion that affect modulation is unlikely during deep sedation and general anesthesia induced and maintained with propofol.

Future directions

Throughout this thesis and discussion of main findings, suggestions for future research have been proposed. Foremost, new studies could clarify whether special attention for individual differences in memory function and expressions of memory is warranted. Needless to say, the study of predictor variables in this thesis should be regarded as exploratory in nature but even so, interesting findings were just as well obtained. Future studies could address potentially relevant determinants of intra-anesthetic memory function such as patient sensitivity to the graded effect of anesthetics. It is a well established fact that large interindividual differences in anesthetic requirements exist and this variation could relate to cognitive plasticity. Patients who require more, for instance, may be expected to have lower thresholds for auditory perception and encoding of acoustic stimuli. Another neurophysiological difference may be found in the make up of individual brains, and novel imaging techniques may shed light on the relevance of variation in brain anatomy and metabolism. Furthermore, it seems relevant to investigate the memory modulatory effect of stress hormones administered or released during anesthesia. Psychological indices of stress and (state) anxiety generally relate poorly to postoperative memory test performance, but physiological studies may shed clear light on this particular variable.

An important implication of this thesis is that future studies should direct effort and attention toward subanesthetic concentrations of anesthesia if they want to address variation in memory function. At lower levels, memory effects are small which imposes a considerable limitation on the statistical power of such studies. Either many patients are to be included or alternatively, a region of anesthetic effect with considerable individual variation in memory function is targeted. In order to refine and validate the model of memory function that was proposed in this thesis, others may prefer to replicate the studies presented here with other anesthetic (and analgesic) drugs combinations.

To conclude, anesthetized patients are far more capable of information processing than their postoperative story tells, yet are not as vulnerable and vigilant as hitherto suggested. Some patients provide for an exception and it is clinically relevant to identify who they are.

Appendix A

A-543

October 15, 2002
9:00:00 AM - 12:00:00 PM
Orange County Convention Center, Room G

Memory Function during Adequate General Anesthesia in Elective Surgical Patients

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Introduction: The probability of memory formation during anesthesia decreases with increasing depth of hypnotic state [1]. Whereas awareness and explicit memory are attenuated by relatively light levels of anesthesia [2], implicit memory may occur at deeper levels. In trauma patients, implicit memory for words primed during adequate anesthesia as measured by bispectral index" (BIS" 40 to 60) has been demonstrated [1]. A large multi-center study found no relation between anesthetic regimen and probability of recall [2], but recall curves for propofol and isoflurane tended to have different shapes. The objective of this study was a) to replicate previous findings [1] in elective surgical patients, and b) to compare the effects of isoflurane and propofol on memory function.
Methods: After Human Investigation Committee approval, 64 consenting patients between age of 18 and 64 were randomly assigned to one of two groups, propofol-based maintenance group (P-group) or isoflurane maintenance group (I-group). No premedication was given. Fentanyl (2g/kg) and propofol (1.5-2.5mg/kg) were used for induction of anesthesia in both groups. During maintenance anesthesia was titrated to BIS" (v3.4, A1050, Aspect Medical Systems, Newton, MA) between 40 and 60, during which 2 sets of word lists out of 4 were randomly primed to patients via headphones. After recovery a word stem completion task (WSCT) was administered, and conscious and cued recall were assessed. In the inclusion part of the WSCT, patients were presented with word stems from 1 primed and 1 non-primed word list, and instructed to complete stems with words during anesthesia or the first word coming to mind in case recall failed. In the exclusion part, they were likewise presented with word stems from other 2 lists and instructed *not* to use words primed during anesthesia. MANOVA was used to analyze mean number of hits for primed and non-primed words in the 2 conditions of the WSCT. ($P<0.05$)
Results: P-group and I-group did not differ in age, weight, height, surgical time and anesthetic time. There was no spontaneous conscious recall. During the WSCT, 8 patients in P-group recalled 31 words, (3 correct, 28 incorrect). In I-group 8 patients recalled 32 words (6 correct, 26 incorrect). Mean hit numbers in the WSCT did not differ significantly in bith P-group and I-group. (Table)
Discussion: In this study, there was no evidence of explicit and implicit memory for words primed during propofol or isoflurane anesthesia. We conclude that memory function in elective surgical patients is unlikely during adequate hypnotic state as monitored by BIS".
References: 1.Anesthesiology 1999;90:670 2.Anesthesiology 1997;86:836

Table: Mean hits and SD

	Inclusion Primed	Inclusion Non-primed	Exclusion Primed	Exclusion Non-primed
P-group	2.56±1.63	2.44±2.00	2.06±1.05	2.22±1.64
I-group	2.25±1.19	2.38±1.16	2.16±1.44	2.50±1.63

2002 ASA Meeting Abstracts.

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Samenvatting

In een medische setting zoals het ziekenhuis heeft anesthesie (narcose) als belangrijk doel patiënten te vrijwaren van herinneringen aan een operatie. De toediening van slaapmiddelen verlaagt het bewustzijnsniveau waardoor de kans op bewuste herinneringen aanzienlijk afneemt en al snel nihil is. Afwezigheid van bewust geheugen betekent echter geenszins dat er geen informatie is verwerkt of is opgeslagen. Het is bekend dat slechts een klein deel van wat wij waarnemen toegankelijk is voor het bewustzijn, terwijl latent aanwezige informatie ons gedrag wel kan beïnvloeden. Een dergelijke invloed duidt erop dat informatie wel degelijk is verwerkt, maar alleen niet wordt herinnerd. In dat kader wordt onderscheid gemaakt tussen bewust (expliciet) geheugen en onbewust (impliciet) geheugen. Ook voor informatie aangeboden tijdens anesthesie is impliciet geheugen gevonden. Een belangrijke klinische vraag is of zulke effecten onbewust ontstaan of door toedoen van onvoldoende anesthesie en daarmee tijdelijk bewustzijn van de patiënt. Een eenduidige maat voor bewuste- dan wel onbewuste informatieverwerking ontbreekt echter tot op heden.

Dit proefschrift onderzocht de relatie tussen geheugenfunctie tijdens anesthesie en de bewustzijnstoestand van patiënten met behulp van een nieuwe maat voor de diepte van hypnose (slaap), de bispectraal index (BIS). Deze index wordt afgeleid van het electroencephalogram (EEG) en varieert van 0 (geen hersenactiviteit) tot 100 (wakker). Het onderzoek richtte zich op twee specifieke niveaus, BIS tussen de 40 en 60 (aangeduid als 'algehele anesthesie') en BIS tussen de 60 en 70 ('diepe sedatie'). Daarbij werd verondersteld, op basis van klinische gegevens, dat het eerstgenoemde niveau een diepere slaaptoestand impliceert dan het laatgenoemde niveau. Voorts werd gebruik gemaakt van een relatief nieuwe testprocedure voor geheugen welke inzicht kan geven in de mate van bewustzijn die aan de testprestatie ten grondslag ligt. Met deze "process-dissociation procedure" (PDP) werden deelnemers in de ene helft van de test geïnstrueerd om woorden aangeboden tijdens anesthesie te gebruiken terwijl dergelijke woorden in een ander deel dienden te worden vermeden. Het uitgangspunt is dat de mate waarin deze contrasterende instructies kunnen worden opgevolgd indicatief is voor bewuste dan wel onbewuste informatieverwerking: de eerste vorm ondersteunt het opvolgen van de instructies (een selectieve reactie), de tweede vorm van verwerking niet.

Voorts werd onderzocht of geheugenfunctie beïnvloed wordt door het type informatie dat wordt aangeboden. Daarbij ging de aandacht uit naar emotionele versus niet-emotionele (neutrale) informatie. Studies geven aan dat beide verschillend worden verwerkt en opgeslagen in het geheugen, ook onder omstandigheden van verminderde bewuste waarneming. In zulke situaties lijken met name emotionele stimuli van invloed. Tijdens anesthesie is hiervoor echter tot op heden geen evidentie gevonden, maar de gebruikte onderzoeksmethoden zijn mogelijk te complex geweest. Daarom werd in het huidige onderzoek een eenvoudig paradigma overgenomen van laboratoriumstudies met normale (wakende) proefpersonen, en werd een simpele emotionele stimulus (een positief geluid) gekoppeld aan weinig betekenisvolle woorden teneinde de emotionele lading van de woorden te beïnvloeden. Aldus werden in twee studies (hoofdstuk 2 en 3) alleen neutrale stimuli gebruikt en in twee andere (hoofdstuk 5 en 6) zowel neutrale als emotionele stimuli. De bewustzijnstoestand van patiënten tijdens stimulusaanbieding werd per studie gecontroleerd en over studies gevarieerd.

Alle onderzoeken werden uitgevoerd met medewerking van relatief gezonde patiënten die een kortdurende ingreep in dagbehandeling ondergingen. Alle deelnemers werden preoperatief geïnformeerd over het onderzoek en stemden schriftelijk in met deelname. Een intraveneus anestheticum (propofol) diende ter inductie van anesthesie en werd ook gebruikt voor het onderhoud. Voorts kregen patiënten bij inductie standaard pijnstilling toegediend en daarna op individuele basis. In alle gevallen werd tevens een neuromusculair block (spierverslapping) toegepast, waarna de longen mechanisch werden geventileerd. Zodra de beoogde diepte van anesthesie was bereikt, bewaakt middels BIS, startte de herhaalde auditieve presentatie van stimuli middels cassettebandje of computer en een gesloten hoofdtelefoon. Elke studie had een experimenteel karakter en bevatte een controlegroep (between-subjects design) of controle conditie (within-subjects design). Zowel onderzoeker als patiënten waren ten tijde van het onderzoek niet op de hoogte van de indeling in groepen en condities. Een paar uur na de operatie, alvorens zij het ziekenhuis verlieten, werden deelnemers ondervraagd en getest op effecten van de manipulatie met behulp van verschillende taken .

Hoofdstuk 2 beschrijft de eerste uit een reeks van vier studies die in het kader van dit proefschrift werden uitgevoerd. Dit onderzoek richtte zich op geheugenfunctie tijdens algehele anesthesie (BIS 40 tot 60). Naar voorbeeld van twee eerdere studies van de Rotterdamse onderzoeksgroep, waarin geheugeneffecten waren gevonden voor een aantal relatief bekende categorie-exemplaren (banaan, peer, groen, geel), werden 82 patiënten (44 mannen) willekeurig toegewezen aan een experimentele groep ($n = 41$) of een controle groep ($n = 41$). De eerste groep luisterde kort nadat de operatie was begonnen 30 maal naar de vier woorden, terwijl de controle groep vogelgezang kreeg gepresenteerd. De groepen waren vergelijkbaar op relevante variabelen, zoals de gemiddelde BIS tijdens stimuluspresentatie (rond de 45) en de duur van anesthesie. Geen van de patiënten had postoperatief bewuste herinneringen aan de operatie of gepresenteerde stimuli, noch werden de aangeboden woorden herkend (recognitietaak). In tegenstelling tot het eerdere onderzoek, waarin niet was gecontroleerd voor de bewustzijnstoestand van patiënten tijdens woordaanbieding, werd in deze studie geen effect gevonden op de indirecte geheugentaak:

patiënten uit de experimentele groep waren niet geneigd de vier intraoperatief aangeboden woorden vaker als fruitsoort of kleur te noemen dan patiënten uit de controle groep. Aldus vonden we in deze eerste studie geen evidentie voor geheugenfunctie tijdens algehele anesthesie waarbij het bewustzijnsniveau van patiënten was bewaakt met behulp van BIS.

In **hoofdstuk 3** werd geheugenfunctie onderzocht bij 56 patiënten (31 mannen) tijdens diepe sedatie (BIS 60 tot 70). Daartoe kregen zij, vlak voordat hun operatie begon maar terwijl slaapmiddelen al werden toegediend, een serie (22) alledaagse Nederlandse woorden te horen. Elk woord werd 10 maal herhaald en voordat een nieuw woord begon werd bepaald of de patiënt bij bewustzijn was door hem of haar het te verzoeken in de hand van de onderzoeker te knijpen (ook wel "commando" genoemd). Een dergelijke procedure wordt vaker toepast in klinisch onderzoek en wordt door sommige clinici gebruikt tijdens operaties waarbij de diepte van anesthesie om medische redenen licht is. De gemiddelde BIS tijdens woordaanbieding lag rond de 65 in deze studie. Een aanzienlijk percentage (66%) van de patiënten reageerde op het commando en negen patiënten (16%) rapporteerden postoperatief bewuste herinneringen hieraan. Niemand herinnerde of herkende echter de aangeboden woorden. Desalniettemin was de subgroep met bewuste herinneringen in staat de woorden te gebruiken dan wel te vermijden in een woordaanvultaak, hetgeen duidde op een zwak, maar bewust tot stand gekomen (expliciet) geheugeneffect van de woordaanbieding tijdens anesthesie. Patiënten zonder herinneringen aan de commando's vertoonden geen dergelijk geheugeneffect. Voorts hingen scores op de postoperatieve taak positief samen (r = 0.35) met scores die preoperatief waren behaald op een zelfde taak, hetgeen suggereert dat patiënten bij wie het geheugen überhaupt goed functioneert ook meer geheugen ontwikkelen tijdens anesthesie. Tenslotte bleken patiënten met bewuste herinneringen tijdens anesthesie vaker op de commando's te reageren dan patiënten zonder herinnering. Dit wijst erop dat de mate van bewustzijn samenhangt met geheugenfunctie, maar de relatie is niet eenduidig. Zo ontwikkelde slechts één op de vier mensen met bewustzijn, geheugen in deze studie.

Hoofdstuk 4 bespreekt een aantal andere bevindingen uit de voorgaande studie en richt zich in het bijzonder op het signaleren van bewustzijn tijdens anesthesie ('awareness'). Een veelgebruikte methode is het postoperatieve interview, waarbij de patiënt naar bewuste herinneringen wordt gevraagd. Uit ons onderzoek en dat van anderen blijkt dat deze methode de incidentie van awareness onderschat: zo kan een aanzienlijk percentage patiënten reageren op een verbaal commando in de hand van de onderzoeker te knijpen, zonder zich dat later te herinneren. Dit pleit voor het bewaken van de bewustzijnstoestand *tijdens* anesthesie. In dat kader werd in hoofdstuk 4 geëvalueerd in hoeverre fysiologische variabelen, zoals hersenactiviteit (EEG variabelen), bloeddruk en hartslag (hemodynamische variabelen), in staat zijn bewustzijn te signaleren. Daartoe analyseerden we de EEG- en hemodynamische data die waren geregistreerd tijdens de meer dan 1000 commando's die we gaven in het voorgaande onderzoek, en bekeken of zij onderscheid maakten tussen een reactie op het commando (de patiënt is bij bewustzijn) en de afwezigheid daarvan (de patiënt slaapt). In tegenstelling tot hartslag en bloeddruk bleken EEG parameters, waaronder BIS, bijzonder goede indicatoren van bewustzijn te zijn. Dit onderstreept de waarde van nieuwe technologische ontwikkelingen op het gebied van bewustzijnsbewaking. EEG variabelen onderscheidden echter niet tussen patiënten met en zonder bewuste herinneringen, wat aangeeft dat deze maten niet zozeer geschikt zijn om geheugenfunctie te bewaken. Voorts besteedt dit hoofdstuk aandacht aan de ervaringen van patiënten met bewuste herinneringen en worden klinische aanbevelingen gedaan. Zo leidt het openlijk bespreken van awareness op voorhand niet noodzakelijkerwijs tot verontrusting bij patiënten, en is het belangrijk (geruststellende) feedback te geven op het moment dat awareness zich voordoet. Dit helpt patiënten te begrijpen wat er gebeurt en lijkt hen te behoeden voor reactieve neurotische symptomen en nare herinneringen.

In **hoofdstuk 5** verschuift de aandacht van het onderzoek naar de verwerking van emotionele stimuli en wordt wederom een studie gepresenteerd tijdens algehele anesthesie (BIS 40 tot 60). In dit onderzoek kregen 38 patiënten (24 mannen) kort na het begin van de operatie 12 betekenisloze (onzin) woorden aangeboden alsmede 12 bestaande Nederlandse woorden die eerder in hoofdstuk 3 waren gebruikt. De helft van beide woordsets werd gepresenteerd in combinatie met een positief geluid dat patiënten voor de operatie hadden uitgekozen (affectieve priming conditie), terwijl de andere helft werd aangeboden zonder het geluid (controle conditie). De gemiddelde BIS tijdens stimulusaanbieding was vergelijkbaar (46 à 47) voor de beide condities. Na de operatie voerden patiënten allereerst een woordaanvultaak uit die alleen betrekking had op de Nederlandse woorden. Iedereen vulde 24 woordstammen, waarvan de helft overeen kwam met de intraoperatief aangeboden woorden, aan met het eerste woord dan in hen opkwam. Vervolgens beoordeelden patiënten elk van de gepresenteerde woorden plus een aantal niet-gepresenteerde woorden op de mate waarin het een positief, prettig gevoel opriep. Daarbij werd een eenvoudige 6-punts (Likert) schaal gebruikt. Niemand herinnerde zich iets van de operatie of stimuluspresentatie. De kans dat mensen een woordstam aanvulden met een woord aangeboden tijdens anesthesie was vergelijkbaar met de kans dat ze het woord noemden zonder aanbieding tijdens anesthesie. Aldus werden in deze studie geen geheugeneffecten gevonden en het koppelen van een positief geluid aan een deel van de woorden maakte hierin geen verschil. Voorts beoordeelden mensen de aangeboden woorden –al dan niet in combinatie met een positief geluid– niet positiever dan de niet-aangeboden woorden en daarmee werd in deze studie evenmin evidentie voor emotionele informatieverwerking tijdens algehele anesthesie gevonden.

In **hoofdstuk 6** wordt de vierde en laatste studie in het kader van dit proefschrift besproken. Dit onderzoek kwam in grote lijnen overeen met de voorgaande studie maar vond ditmaal plaats tijdens diepe sedatie (BIS 60 tot 70). In tegenstelling tot het eerdere onderzoek werd in deze studie alleen een deel (6) van de (12) onzinwoorden tijdens anesthesie met een positief geluid aangeboden, terwijl de (12) bekende Nederlandse woorden 10 maal werden herhaald. In navolging van het onderzoek beschreven in hoofdstuk 3, werd postoperatief het geheugen onder andere getest met behulp van de proces-dissociatie procedure waarbij deelnemers in de ene helft van de (woordaanvul-)taak aangemoedigd werden woorden aangeboden tijdens anesthesie te gebruiken terwijl zij dergelijke woorden in een ander deel dienden te vermijden. Voorts werd tijdens anesthesie een aantal maal bepaald of patiënten bij bewustzijn waren door ze te vragen in de hand van de onderzoeker te knijpen, en werd preoperatief een aantal taakjes afgenomen. In aanvulling op eerder onderzoek (hoofdstuk 3), bevatte dit onderdeel behalve visuele- ook een tweetal auditieve taken. Van de 30 deelnemende patiënten (18 vrouwen) konden 20 preoperatief worden getest. Gedurende de periode van stimulusaanbieding tijdens anesthesie was BIS gemiddeld 62 en 64 (bekende versus onzin woorden). Weer reageerde een aanzienlijk percentage (60%) van de patiënten op commando's, maar ditmaal rapporteerden slechts 2 patiënten (7%) achteraf bewuste herinneringen. Niemand herinnerde zich, of herkende, de aangeboden woorden. Patiënten bleken niet in staat deze woorden te gebruiken dan wel te vermijden in de woordaanvultaak. Scores op deze taak hingen in gelijke mate als eerder werd geobserveerd (hoofdstuk 3) samen met preoperatieve geheugenscores en ondanks het beperkte aantal deelnemers vonden we sterke aanwijzingen dat auditieve taken een betere voorspeller van verschillen in postoperatieve geheugenprestatie zijn dan visuele taken. Onzinwoorden aangeboden met een positief geluid werden niet positiever beoordeeld dan woorden niet aangeboden met een dergelijk geluid of dan niet-aangeboden woorden. Aldus kon in deze studie noch geheugenfunctie noch emotionele informatieverwerking worden aangetoond.

Op basis van het presenteerde onderzoek wordt in **hoofdstuk 7** een aantal conclusies getrokken ten aanzien van de vraagstellingen die ten grondslag lagen aan dit proefschrift. Ten eerste ondersteunen de bevindingen een relatie tussen geheugenfunctie tijdens anesthesie en de bewustzijnstoestand van patiënten. Dit bleek enerzijds uit het patroon van geobserveerde effecten over de vier studies, waarbij geheugenfunctie alleen tijdens het lichtere slaapniveau (diepe sedatie) kon worden aangetoond. Anderzijds bleek de mate waarin patiënten reageerden op een verbaal commando tijdens diepe sedatie samen te hangen met het optreden van geheugen, maar eenduidig was deze relatie niet. Voor specifieke richtlijnen met het oog op de individuele patiënt is het dan ook nog te vroeg. Wel kan op basis van de huidige stand van zaken een aantal niveaus van slaap (BIS) worden onderscheiden, waarbij een toename in diepte van hypnose gekenmerkt wordt door een afname in bewustzijn en geheugenfunctie. In tegenstelling tot veel eerder onderzoek waarin diepte van hypnose niet zozeer werd bewaakt, geeft dit proefschrift aan dat geheugenfunctie is uitgeschakeld bij gecontroleerde, adequate hypnose. Daarmee is het niet onwaarschijnlijk dat een aanzienlijk aantal positieve bevindingen in dit veld van onderzoek tot nog toe het gevolg zijn geweest van inadequate hypnose. Het is echter belangrijk op te merken dat specifieke situaties en patiëntkarakteristieken een uitzondering op de regel kunnen vormen en aanwijzingen hiervoor werden in het gepresenteerde werk gevonden. Teneinde risicogroepen te identificeren, pleit dit proefschrift voor verder onderzoek naar dergelijke factoren en meer aandacht voor individuele verschillen.

De veronderstelling dat emotionele informatie sneller en beter wordt verwerkt dan niet-emotionele informatie in situaties waarbij het bewustzijn is uitgeschakeld of verminderd, wordt niet ondersteund door de resultaten van het huidige onderzoek. Met een vernieuwde methode van aanpak, geënt op belangrijke studies uit het laboratorium, werd desalniettemin geen evidentie gevonden voor de verwerking van emotionele stimuli. Dit bevestigt de controverse die in het algemeen bestaat over emotionele informatieverwerking tijdens anesthesie. Vooralsnog lijkt het erop dat patiënten niet noodzakelijkerwijs emotioneel kwetsbaar terwijl zij worden geopereerd. Aangezien met merendeel van klinische studies –inclusief de twee die in het kader van dit proefschrift werden uitgevoerd– gebruikt maakt van positieve affectbeïnvloeding, kan niet worden uitgesloten dat negatieve informatie wel van invloed is op het welbevinden van patiënten en geheugenfunctie tijdens anesthesie. Vanuit theoretisch oogpunt roepen de geobserveerde nulbevindingen interessante vragen op over de minimale vereisten voor het ontstaan van emoties en de rol van bewustzijn hierin.

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Curriculum Vitae

Chantal Kerssens was born on April 15, 1971 in Alkmaar, The Netherlands. She grew up in nearby Heerhugowaard, where she graduated from high school (Atheneum) in 1989. After attending the Vrije Hogeschool in Driebergen for one year, she studied psychology at the University of Amsterdam. Here, she soon became actively involved in the organization of the curriculum and, as student member, participated in various councils and boards over the years. In August 1996, having studied residual auditory perception in surgical patients under general anesthesia, she graduated with honors in Psychonomics. Shortly thereafter, she took up a position as research associate at Emory University School of Medicine (Atlanta, GA, USA) to pursue her interest in memory function during anesthesia. She continued this line of research a year later at Erasmus MC in Rotterdam, working in joint collaboration at the departments of Medical Psychology & Psychotherapy and of Anesthesiology. The results of these studies gave rise to this thesis. She part-time assisted in the development of a new medical curriculum and lately supervised research into allo- and xenotransplantation. In the fall of 2002, she will return to Emory University as an Instructor in Anesthesiology and Lecturer in Psychology. Her research will concentrate on determinants of memory function during anesthesia and postoperative recovery.

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