MEMORY DURING GENERAL ANAESTHESIA: VARIATIONS IN STIMULUS CHARACTERISTICS

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MEMORY DURING GENERAL ANAESTHESIA: VARIATIONS IN STIMULUS CHARACTERISTICS

Geheugen tijdens algehele anesthesie: variaties in stimulus karakteristieken

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"Your memory is like a monster; *you* forget - *it* doesn't. It simply files things away. It keeps things from you, or hides things from you - and summons them to your recall with a will of its own. You think you have a memory; but it has you!"

John Irving, 1989

Voor Ruud en voor mijn opa, Joseph Gosschalk

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Preface

This thesis is the description of a research project into memory and perception during general anaesthesia. The question whether surgical patients can hear and process information without awareness (i.e., during general anaesthesia) is adressed on the basis of psychological research into information processing during general anaesthesia (see Chapter 1). The general aim of this work is to determine if and when memory and perception takes place during general anaesthesia. Assessment of the experimental circumstances under which unconscious functioning is preserved in anaesthetized patients (Chapters 4 and 5) has important implications both for clinical practice and for psychological theories of memory.

The project is the result of the fruitful collaboration between the Department of Medical Psychology and Psychotherapy of Erasmus University Rotterdam, and the Departments of Anaesthesiology and General Surgery of St. Clara's Hospital Rotterdam. The work presented in this thesis was made possible by grant 900-559-027 from the Dutch Organisation for Scientific Research (NWO). NWO made it possible to present the findings of this project at different congresses. Financial support for the publication of this thesis was made possible by NWO and the Erasmus University Rotterdam.

In the first chapter of this thesis, the literature on memory during anaesthesia is discussed. This chapter was written during the last months of the project. For this reason, the review includes two of the studies that were conducted within the context of the whole research project. At the moment this thesis was prepared, a shortened version of Chapter 1 was prepared for publication; the study described in Chapter 3 was published in *Anaesthesia* (1993, 48:657-660); and a manuscript of the studies described in Chapters 4 and 5 was submitted to *Memory and Cognition*.

CHAPTER 1

Memory during general anaesthesia: practical and methodological aspects.

A.E. Bonebakker, M. Jelicic, J. Passchier, and B. Bonke

Abstract

Evidence from studies of memory and awareness during general anaesthesia suggests that some form of cognitive functioning is preserved in surgical patients. This finding has important implications both for clinical practice and for psychological theories of memory. In order to give the methodological background of the present situation in this field of research, this article deals, on the basis of recent experiments, with important methodological aspects of studies into perception and memory during general anaesthesia.

Introduction

During the past decade, memory for information presented during general anaesthesia has been extensively investigated. Ever since the investigators Cheek[1] and Levinson[2] reported in 1959 and 1965 that patients, under hypnosis, could recall conversations and incidents that presumably had taken place during anaesthesia, researchers in the field have investigated the possibility that under some circumstances, anaesthetized patients may process information that was presented intraoperatively. Some studies yielded positive results, others did not. Nevertheless, memory for intraoperatively presented material could not be demonstrated convincingly. In 1992, at the Second International Symposium on Memory and Awareness in Anesthesia[3], about half of the relevant studies had yielded positive results, half nonsignificant findings[4-7]. Although the experimental designs of the studies had become more and more sophisticated in comparison with the first congress on the topic three years earlier[8], the findings were still very inconsistent. Due to more advanced techniques to measure memory processes there now seems to be more reliable evidence that memory for events during anaesthesia does occur. This does not yet mean that we are dealing with a more or less established truth. Much work still needs to be done, especially with regard to the assessment of anaesthetic adequacy and the development of a theoretical framework that satisfactorily explains the body of data coming from studies into memory in general anaesthesia.

On the basis of a selection of studies, we will discuss a number of practical and methodological issues associated with this line of research. The studies include implicit-memory studies and studies into the effects of therapeutic or behavioural suggestions presented during anaesthesia. For a more complete overview of the area, the reader is referred to a number of excellent review articles[9-11] and to the proceedings of the First and Second International Symposia on Memory and Awareness in General Anaesthesia[3,8].

The history so far

The question whether or not surgical patients can process information or even 'be aware' during general anaesthesia has occupied anaesthesiologists for a long time (by definition, general anaesthesia is a state of unconsciousness). 'Awareness' however, implies a state of consciousness, of alertness or perception, which does not go together with general anaesthesia: "... a patient under general anaesthesia cannot be aware and the converse is equally true; an aware patient is not anaesthetized" (quoted from Payne[12], p. 38). However, with the introduction of muscle relaxants by Griffith and Johnson in 1942[13], which reduced the need for deep anaesthesia, anaesthesiologists began to suspect that some patients might be conscious during surgery. In 1947, Harroun, Beckert, and Fisher[14] suggested that some patients might remember distressing intrasurgical events. This would imply that patients might sometimes be awake during surgery, and perhaps also have pain, while unable to communicate in any way due to the paralyzing effects of muscle relaxants. Even in the 19th century, Claude Bernard described vividly how it feels to be conscious while paralyzed (now referred to as 'awareness'), when he described the effects of curare on the conscious subject: "... Can you imagine a more dreadful agony than that of a mind conscious of the loss of control over those organs designed to serve it and finding itself fully alive entombed in a corpse?"[15] (as quoted by Payne[12], p. 39).

Not until 1959 was the issue of awareness during general anaesthesia again addressed in the scientific literature. It was then that the American gynaecologist Cheek described patients who postoperatively showed signs of anxiety or depression, or recovered poorly, without an obvious cause. According to Cheek, these patients could later, in hypnosis, repeat offending or threatening remarks (sometimes even verbatim) made by the surgical team[1]. Levinson's notorious imitation of a surgical crisis was another attempt to call attention to the possibility of memory for intraoperative events[2]. He subjected ten volunteer patients undergoing minor surgery under general anaesthesia to a simulated crisis, in which the anaesthesiologist stated that the operation had to stop because the patient had turned blue and needed more oxygen. One month later, these patients were hypnotized and age-regressed to the time of surgery. It then appeared that four of the ten patients were able to repeat almost exactly the words of the anaesthesiologist; four others remembered having heard something, and some of them recognized the voice of the anaesthesiologist[2]. Although the reactions of these patients are quite outspoken it is difficult to evaluate the validity and impact of this study that many would nowadays consider unethical; Levinson himself hypnotized the patients while he knew what had happened during surgery, thus being able to influence the patient's behaviour under hypnosis. However, it seems unlikely that this explains the outspoken reactions of the patients.

Ten years later, the question whether patients could recall intraoperative events was again raised by Trustman, Dubovsky, and Titley[16], who critically reviewed seven studies. They concluded that all seven experiments had methodological shortcomings and, therefore, that evidence for auditory perception during anaesthesia either did not exist, or was an artifact of improper technique. Then, shortly after this publication, Tunstall[17] introduced the isolated forearm technique (IFT) as a method to assess directly the presence or absence of information processing during anaesthesia. This technique involves inflating a blood-pressure cuff around the patient's arm before injection of neuromuscular blockers, but after induction of anaesthesia, so that the arm may be moved in response to verbal instructions. Tunstall[17], and later also Russell[18], reported intraoperative awareness by means of this technique in most of the patients in their studies. However, there are some practical and technical problems related to the use of IFT[10], which makes results coming from most IFT studies difficult to interpret; response to command using this technique tends to correlate poorly with clinical signs of light anaesthesia[19] and it appears difficult to distinguish purposeful arm movements from reflex movements[20,21]. Nevertheless, the interest in (possible) memory processes during general anaesthesia was growing, and Millar and Watkinson's[20] finding of recognition memory for words presented during surgery, as well as Bennett, Davis, and Giannini's[22] study on postoperative motor responses made clear that some information-processing might indeed be going on during general anaesthesia.

Since 1977, the research into this topic has increased exponentially. Rather than using hypnosis to assess memory for the intraoperative period, investigators now place emphasis on the use of sensitive tests of memory, postoperative recovery, and motor behaviour.

Unconscious processes

At approximately the same time when research into memory and awareness in anaesthesia was expanding, attention in the field of memory shifted from the study of conscious memory processes to that of unconscious processes[23,24]. Experimental research, mainly in amnesic patients, made clear that information stored in memory during a particular episode can influence later behaviour *without* conscious recollections of that episode[25,26].

In memory research a theoretical distinction is made between implicit and explicit memory, terms introduced by Graf and Schacter[27]. 'Implicit memory' refers to memory performance that does not require recollection of previous learning experiences. In contrast, 'explicit memory' refers to the conscious recollection of previous experiences. This is the kind of memory most of us are familiar with, and the kind of memory responsible for 'awareness' experiences during general anaesthesia. It is important to note that implicit and explicit memory are merely descriptive terms to classify memory processes, *not* to relate specific memory systems to performance on specific tasks[27,28]. On the basis of the implicit/explicit memory distinction, a number of direct and indirect tasks have been developed to study memory processes. Direct and indirect tasks of memory.

Examples of 'direct' tests of memory are tasks of 'free recall', 'cued recall'-, and 'recognition'. In free-recall tasks, subjects are asked to retrieve previously presented information from memory without any specific test cues given. In cued-recall tasks, cues (e.g., the first letter of a word) are presented to stimulate recall of certain information. In recognition tasks, subjects are presented with both old (that is, presented earlier) and new information and requested to indicate the 'old' information. In direct tasks, subjects are instructed to think back to the study phase in order to recollect previously presented information.

In a typical indirect memory task, memory for previously presented information is assessed by asking subjects to perform a simple task, for example, complete word stems (the first two or three letters of a word, like 'PEN...'). Subjects are instructed to complete these stems with the first word that comes to mind (e.g., 'PENSION'). This particular instruction is important because: a) no reference is made to a previous learning phase, and b) encouraging subjects to name the first thing that comes to mind taps 'activated' information in memory that corresponds with the presented items[29].

With regard to the anaesthesia research, these memory tasks can be applied as follows: during general anaesthesia, i.e., during the *learning-phase*, stimuli are presented verbally (via headphones) to surgical patients. Postoperatively, i.e., in the *test-phase*, patients are requested to perform a task pertaining to the intraoperatively presented material. Indirect tasks are particularly useful in assessing memory and perception in general anaesthesia because patients are not required to consciously recollect a learning episode (e.g., presentation of information during anaesthesia), but memory for the information is inferred from altered performance on the indirect test.

At first, in the sixties and seventies, studies into memory in anaesthesia were performed by means of direct tasks. In other words, conscious memory for intraoperative events was studied. These studies were not very successful, presumably because information is poorly encoded during the state of unconsciousness induced by general anaesthesia[30]. In other words, during anaesthesia, minimal or no attention can be paid to presented information. Consequently, and under normal circumstances, patients do not have conscious memories of intraoperative events. On the other hand, this temporary blockage of consciousness does allow investigators to assess unconscious memory processes. Within the field of memory in anaesthesia, research has concentrated on these unconscious processes which appear to be more accessible by means of indirect memory tasks, and by the intraoperative presentation of therapeutic and behavioural suggestions. In particular, studies using these types of research methods have revealed evidence of unconscious processes during general anaesthesia.

Research methods

Therapeutic suggestions

Egbert, Battit, Welch, and Bartlett[31] reported in 1964 that patients who had been informed about their operation and emotionally supported before surgery, subsequently required less analgesic medication, were in a better mental state, and had shorter hospital stays than controls who had been given minimal information before their operation. Since then, investigators have considered the possibility that intraoperative presentation of therapeutic suggestions (like "Everything is going well, you will feel well after the operation") might have a favourable effect on postoperative recovery. A large number of studies has been conducted yielding conflicting results.

One of the most well-known therapeutic-suggestion studies is the one by Evans and Richardson[32]. These investigators reported a significant effect on postoperative recovery of therapeutic suggestions in 39 hysterectomy patients; their experimental group, which had been presented during surgery with recorded suggestions for faster recovery, fewer postoperative problems, and enhanced feelings of well-being after surgery, left hospital on average 1.3 days earlier than the control group. However, Evans and Richardson did not describe the anaesthetic procedures, and the preoperative 'health status' of the patients had not been determined; patients in the experimental group may have been 'healthier' than patients in the control group (see also Millar[33]). Evans and Richardson's study was later repeated by Liu, Standen, and Aitkenhead[34], who were unable to show an effect of the presentation of suggestions. They added an extra control group consisting of 25 patients who were exposed to a short story about the hospital where the patients were being treated in order to control for any simple beneficial effects of a voice during surgery. The whole sample consisted of 73 hysterectomy patients, who either received positive suggestions like Evans and Richardson's, a short story about the hospital, or a blank tape. There were no differences between their groups with respect to the outcome variables. Millar[33] reanalyzed these two studies and concluded that the control group in the Evans and Richardson study differed significantly from the other groups with respect to postoperative recovery. Millar suggests that these patients recovered slower because they were physically less well compared to the other groups. For this reason the effect in Evans and Richardson's study may have been due to chance bias in allocation of patients to this control group making it uncertain whether positive suggestions have a reliable influence upon the recovery measure 'days to discharge'.

A study by Bonke, Schmitz, Verhage, and Zwaveling[35] among 91 surgical patients revealed that older patients who had been played positive suggestions during surgery, had a shorter postoperative stay than two comparison groups. However, other indices (i.e., pain scores, subjective well-being scores, and nurses' ratings) did not differ among their groups. A modified replication of this study by Boeke, Bonke, Bouwhuis-Hoogerwerf, Bovill, and Zwaveling[36] only yielded a nonsignificant trend. Woo, Seltzer, and Marr[37] likewise found no effect of suggestions but their study was methodologically flawed[38].

Steinberg, Hord, Reed, and Sebel[39], following a similar, original study by McLintock, Aitken, Downie, and Kenny[40] investigated both postoperative well-being and postoperative analgesic requirements. In both studies, 60 patients (hysterectomy or breast-surgery) were presented during anaesthesia, with either positive suggestions or a blank tape. In the postoperative phase, pain-medication was self-administered by the patients by means of a Patient Controlled Analgesia device (PCA). This latter measure (i.e., amount of medication as provided by PCA) was then considered an objective and promising method to assess the effects of suggestions on postoperative pain sensations. McLintock et al. found that their suggestion group required on average fewer analgesics (51.0 mg morphine in 24 hrs) than their control group (65.7 mg). In the study by Steinberg and co-workers comparable differences were found (see also Caseley-Rondi, Merikle, and Bowers[41], and Van der Laan, Van Leeuwen, Sebel, Winograd, Bauman, and Bonke[42], submitted, who found no effect).

Bethune, Gosh, Walker, Carter, Kerr, and Sharples[43] found a positive effect on duration of hospital stay of intraoperative presentation of positive suggestions. They presented 51 patients (undergoing cardiac surgery) with either positive suggestions, or the suggestion to later touch their ear (see below), or a blank tape during three different types of anaesthesia. Mean duration of hospital stay was 7.8 days in the therapeutic suggestion group, which differed significantly from that in the other two groups (9.5 and 9.2 days, for behavioural suggestion- and blank tape, respectively).

Jelicic, Bonke, and Millar[44] investigated the effects of different types of therapeutic suggestions, i.e. affirmative ("You will feel well") and nonaffirmative ("You will *not* feel sick"). The relevance of nonaffirmative suggestions or remarks made by clinicians is the implication of a negative or threatening possibility ("You do *not* have cancer") which may make patients anxious ('let sleeping dogs lie ...') and consequently have a negative effect on their well-being. Jelicic and colleagues found a favourable effect of the presentation of mixed suggestions (affirmative and nonaffirmative) on postoperative hospital stay as compared with the other groups (affirmative, nonaffirmative, and blank tape, respectively). No such effect was demonstrated for subjective well-being. Because there were no effects of either affirmative or nonaffirmative suggestions, i.e., "...the 'ingredients'..." (quoted from Jelicic et al.[44], p.347) it is difficult to interpret the results of this study. Jelicic and colleagues suggested that their findings might be due to chance[44].

It is conceivable that individuals differ in their susceptibility to therapeutic suggestions presented during surgery. In two recent suggestion-studies, the possible relation between hypnotizability and susceptibility to suggestions was taken into account. Korunka, Guttmann, Schleinitz, Hilpert, Haas, and Fitzal[45] presented 163 gynaecological patients during general anaesthesia with either therapeutic suggestions, music (preferred by the patients), or previously taped operation-room sounds (double blind). Hypnotizability was measured by the Stanford Hypnotic Susceptibility Scale[46]. Indirect measures of any beneficial effects of the therapeutic suggestions were postoperative analgesic requirements, subjective pain sensations, and duration of postoperative hospital stay. Recall and recognition of the intraoperative stimuli were assessed by questioning patients during hypnosis and presenting them with excerpts of the intraoperative tapes. Half of the patients did not recognize the tape-excerpts, but of those who did, the majority correctly identified the tape they had been played. The investigators found a beneficial effect of intraoperative presentation of positive suggestions and music on postoperative analgesic requirements and duration of hospital stay. However, there was no evidence indicating that suggestibility might have been a determinant of the obtained results. Likewise, Caseley-Rondi, Merikle, and Bowers[41] studied the beneficial effects of therapeutic suggestions on postoperative well-being and morphine consumption, and the relevance of hypnotizability on the processing of information under anaesthesia. Ninety-six patients, undergoing elective abdominal hysterectomy, were presented with either therapeutic suggestions, or melodies, or suggestions plus melodies, or silence. It was shown that patients in the suggestions group used a significantly smaller amount of morphine than patients who were not played suggestions. Hypnotizability was not significantly associated with therapeutic outcome, but interestingly, high- but not low-hypnotizable patients appeared to be very accurate in their guesses whether or not they had been played suggestions. No evidence for memory of melodies was found.

In general, the results of studies into the effects of therapeutic suggestions have not been consistent. Four of the twelve studies reported here yielded non-positive findings[34,36,37,42], and two yielded effects that could not be explained easily[35,44]. Replication of one of the five studies that yielded beneficial effects of suggestions[32] was unsuccessful[34] indicating the absence of compelling evidence in the Evans and Richardson study. The main cause of this inconsistent pattern of results is the large variety of dependent variables. Outcome measures are length of postoperative hospitalization, postoperative well-being and recovery, and postoperative analgesic requirements. Postoperative analgesic requirements and length of hospital stay are relatively objective measures, although the latter may differ across hospitals (depending on the policy of the surgeons). Postoperative well-being is a concept that has been measured in a wide variety of ways across all suggestion studies (see also *Postoperative measurement*) making it difficult to interpret positive results. An alternative explanation for the inconsistent results is that suggestions may be perceived during anaesthesia, but do not result in improved recovery. Our tentative conclusion would be that there as yet no strong evidence that positive suggestions during anaesthesia have a beneficial effect on postoperative recovery and well-being (see also Merikle and Rondi[7]).

Behavioural suggestions

A second method to assess memory for the intraoperative period is the presentation of suggestions during anaesthesia to touch a particular body part (e.g., the ear) during a postoperative interview. Bennett, Davis, and Giannini[22] were the first to use such instructions. They reported that two days after surgery, and even later, patients in the experimental group were more likely to touch their ears than patients in a control group who had not received the suggestions. This study has, however, been widely criticised[9,47], the main criticisms being that close inspection of the data revealed that the differences between experimental and control groups were due to extreme reactions of only two patients, and that any indication of baseline ear-touching behaviour was lacking. In a similar study, Goldmann, Shah, and Hebden[48] found that patients who had been administered the suggestion to touch their chin postoperatively, did so more often than those who had not heard intraoperative messages. Like in the study of Bennett et al., this effect was caused mainly by four of the twenty-one patients in the experimental group[47].

McLintock and colleagues[40] instructed their patients (n=40) to touch their ear in response to a trigger phrase which would be spoken during the postoperative interview. Six hours postoperatively only one patient in the experimental group touched the ear in response to the trigger phrase. Likewise, Jansen, Bonke, Klein, Van Dasselaar, and Hop[49] were unable to find evidence for an increase in ear touching following appropriate intraoperative instructions to do so. Contrary to the other behavioural-suggestion studies these investigators also assessed ear-touching behaviour before the operation in order to obtain baseline ear-touching performance. Moreover, Jansen's patients were interviewed on the first postoperative day instead of some days later, and ear-touching was scored only during a predetermined period of time.

Half the patients in a study by Block, Ghoneim, Sum Ping, and Ali[50] were instructed during anaesthesia, to pull an ear; the other half to touch their nose when they were visited postoperatively. When interviewed within a few hours after surgery, patients reportedly spent significantly more time touching the suggested body part than they did touching a control part. This effect was no longer present on the day after surgery. Merikle and Rondi[7] re-examined the results of this study and concluded that the use of many different measures of memory (Block et al. used three different measures, see also next paragraph), with some measures showing positive and others negative effects, hampers interpretation of the positive findings. Dwyer, Bennett, Eger, and Peterson[51] encouraged 30 of their 45 patients to touch their ear; the remaining 15 patients were instructed to keep their arms still during the postoperative interview. Twenty-four hours after surgery, the number of times each patient touched an ear during the interview was noted. The number of ear-touches did not differ between those who had and had not received the intraoperative instruction to touch their ears. Finally, Bethune and colleagues[43] also found no effect of suggestions on ear-touching behaviour in their comprehensive suggestion-study of patients undergoing cardiac surgery.

Our review of the behavioural-suggestion studies again yields divergent results. The three studies that reported positive effects[22,48,50] had methodological shortcomings. In the studies by Jansen et al.[49], Dwyer et al.[51], and Bethune et al.[43], ear-touching performance did not differ from preoperatively determined 'baseline ear touching'. In summary, none of these studies resulted in convincing evidence that behavioural suggestions presented during anaesthesia are perceived and are capable of changing postoperative motor behaviour.

Indirect memory tasks

More compelling evidence comes from studies in which indirect tasks of memory were employed. Experiments using these tasks are conducted as follows: during surgery single words or small sentences are presented via headphones. Postoperatively, patients are requested to perform a specific task related to the presented words (an indirect task). A number of recent findings will be discussed here, and the reader is referred to Andrade (in press) for a review of other studies.

Category generation: Block et al.[50], beside their behavioural-suggestions test, used two indirect tasks: a) the Word Completion Task, requiring patients during the test-phase to complete word stems that corresponded with the critical stems of words presented during anaesthesia, and b) a Category Generation task, in which patients were given the names of a number of word categories (e.g., 'types of trees') and were asked to name exemplars for each (e.g., 'oak'), after the intraoperative presentation of category exemplars. Block et al. found evidence of implicit memory on word completion, but not on category generation[50].

In contrast, Westmoreland, Sebel, Winograd, and Goldman[52] did not obtain evidence of implicit memory. Their main objective was to investigate the effect of a common tranquillizer, midazolam, on implicit-memory function, as assessed by a Category Generation task. Neither the patients who did, nor those who did not receive midazolam showed a tendency to name the category exemplars presented during anesthesia.

In a series of three studies from the research group in Rotterdam, implicit memory was also assessed by means of the Category Generation task. The first, by Roorda-Hrdlicková, Wolters, Bonke, and Phaf[53] showed that patients (n=81) who had been presented intraoperatively with familiar category exemplars (such as 'yellow' for colours), mentioned these exemplars three times more often than controls who had been presented with seaside sounds. A replication by Jelicic, Bonke, Wolters, and Phaf[54] with a different anaesthetic technique yielded a similar, smaller, but nevertheless significant difference between the two groups. Motivated by these results, Bonebakker, Bonke, Klein, Wolters, and Hop[55] (see Chapter 3) investigated implicit memory with the same task, but with other word categories and less-common exemplars. Eighty-one surgical patients were presented with different combinations of three pairs of category exemplars (i.e., 'musical instruments'-'fish', 'musical instruments'-'birds', and 'birds'-'fish'). Moreover, these words were presented 0, 5, or 30 times to assess a possible effect of number of presentations. No memory effects, and consequently no effect of number of presentations were found. A study which resembles the latter study is that of Brown, Best, Mitchell, and Haggard[56] involving 10 surgical patients, in which the effect on memory of multiple presentations versus a single presentation of words during anaesthesia was studied. Low-frequency versions of 'biased homophones' (like 'hymn' instead of 'him') and infrequent category exemplars were presented either 3 x, 1 x, or 0 x (control) during general anaesthesia. Two days postoperatively, Brown et al. found a marginally significant difference in performance across the three conditions. Mean reproduction of words that had been presented once was slightly above baseline performance (n.s.). Mean reproduction of words that had been presented three times was below baseline. In discussing their findings, Brown and colleagues suggested that information presented more than once under general anaesthesia may be suppressed in a postoperative test because it is associated with aversive intraoperative experiences. However, in this study, words were not presented during surgery, but before the first incision, making the possibility of 'association with an aversive point in surgery' (Brown et al.[56], p. 246) less likely. Moreover, the small sample size in this study and the possible interference from theatre sounds (the headphones were removed after stimulus presentation) make the results from this study less reliable.

Villemure, Plourde, Lussier, and Normandin[57] used two methods to assess auditory information processing during general anaesthesia: intraoperative presentation of category exemplars and registration of Auditory Evoked Potentials (AEPs, see *Depth of anaesthesia* for a more detailed description). During surgery, ten patients were presented with either a list of vegetables or a list of birdnames, containing exemplars varying in representativeness*. Patients were tested 4 and 24 hours postoperatively, and on both occasions evidence of implicit memory was found by means of the Category Generation Task. On the other hand, Villemure et al. were unable to show a clear relationship between the AEP-patterns and implicit memory performance.

Famous Names/Common Facts: in order to investigate possible learning (i.e., establishing new representations in memory) as opposed to activated representations in memory (activation of existing knowledge, see Graf and Mandler[29]) during anaesthesia, one can present patients with 'new' information during anaesthesia. In the Famous-Names Task, patients are presented with fictitious combinations of first and last names during the learning phase. In the test phase, they are again confronted with such combinations of first and last names, some of which were, and others were not presented before, and requested to rate these names as belonging to 'famous' or 'nonfamous' people. Misattribution of fame is taken as evidence of implicit memory for presented names[58]; patients rate fictitious (!) names as belonging to 'famous' people, not because these people are truly famous, but because their names were previously perceived (during anaesthesia). The notion here is that the name 'rings a bell', and in the absence of remembrance, this feeling is attributed to the obvious alternative, i.e., fame.

In the Common-Facts Test patients are presented with the answers to a number of general knowledge questions (of the Trivial-Pursuit type) during the learning phase.

*Representative, or prototypical exemplars of such categories, would be, for instance, 'cabbage' and 'robin'; and less representative: 'zucchini' and 'cormorant'

Subsequently, in the test phase, they are confronted with both the corresponding general knowledge questions and control questions. Implicit memory is demonstrated if more presented than unpresented questions are answered correctly than can be attributed to chance (i.e., baseline performance).

Using this technique, Dwyer et al.[51] found no evidence of implicit memory after intraoperative presentation of *obscure* facts (e.g., "the blood pressure of an octopus is..."). Jelicic, de Roode, Bovill, and Bonke[59] on the other hand, studying 43 patients undergoing eye-surgery, found that patients presented with common (but largely forgotten) facts during surgery, postoperatively answered more corresponding questions correctly than patients who had not been exposed to this material. There was however, a difference between these studies with regard to the complexity of the stimulus material. It is more difficult to respond to "What is the blood-pressure of an octopus?" (Dwyer et al.[51]) than "When did Queen Beatrix come to the throne?" for Dutch patients (Jelicic et al.[59]). In addition, Jelicic and colleagues found that patients who had been presented with fictitious names were postoperatively more likely to rate the presented names as 'famous' than those not exposed to the names. Jelicic, Asbury, Millar, and Bonke[60] found no such effects in a replication study in which a different anaesthetic technique and different stimuli were employed (see also De Roode, Jelicic, Bonke, and Bovill[61]).

Other tasks: Kihlstrom, Schacter, Cork, Hurt, and Behr[62] presented 25 surgical patients with paired associates (i.e., stimulus terms (cues) and the most frequent response, like 'CAT' and 'DOG') during inhalation-anaesthesia. Immediately after surgery, and two weeks later, free and cued recall, and recognition memory were tested. To assess implicit memory for the intraoperative material, patients were presented with one of the words from the paired associates and instructed to name the first word that came to mind (free association). With this task the investigators were able to demonstrate a significant implicit memory effect on both immediate and delayed trials. There was no recognition, nor any free or cued recall of the experimental material.

Schwender, Kaiser, Klasing, Peter, and Pöppel[63] compared three common anaesthetic techniques. They divided 45 patients who underwent cardiac surgery into four groups, in three of which different anaesthetic cocktails were administered. The fourth group served as a control, and the patients in this group were assigned randomly to one of the anaesthetic regimes. During all operations, Auditory Evoked Potentials were recorded and a tape was presented containing the story of Robinson Crusoe. Schwender and colleagues deliberately chose the Robinson Crusoe story because it tells the tale of an individual who overcomes a very difficult situation. According to Schwender, the situation surgical patients find themselves in, is comparable to Crusoe's struggle to survive; that is, patients might identify themselves with the hero. At the end of the text on the tape, patients were instructed to come up with this story during the postoperative interview, 3-5 days later, when invited to free-associate to the trigger word 'Friday'. The aim of this study was to find out which anaesthetics most effectively suppress auditory information processing in general anaesthesia. Schwender and co-workers reported, beside evidence of implicit memory in one of their groups (in group I -receptor specific anaesthesia- 50% of patients gave responses that were associated with the Crusoe story, different effects of their anaesthetic techniques on auditory perception; non-specific anaesthetics which 'anaesthetize' several brain functions, seem to suppress auditory information processing more effectively than receptor-specific agents.

As can be inferred from this review, indirect tasks of memory have been used successfully in seven out of the twelve reported studies[50,53,54,57,59,62,63]. This indicates that there are at least some conditions under which memory for material presented during anaesthesia can be demonstrated. In two out of five studies that did not yield any evidence, plus in Block et al's category-generation condition, complex or unfamiliar verbal material had been used as stimuli[50,51,55]. It is possible that this factor accounts for the null findings in these studies. In other words, the experimental conditions seem to determine the occurrence of memory effects (see also *Type of stimuli and task*).

Theoretical, practical, and methodological aspects

What characterizes the work done so far is an inconsistent pattern of results. This situation might change if there was more uniformity in experimental designs and procedures and if more investigators tried to replicate positive results. Interestingly, hardly any effects have yet been adequately replicated. Without replications, given that the results in this field are far from uniform, evidence for memory in general anaesthesia may still be interpreted as chance findings.

There is growing consensus[64,65] as to which experimental factors are likely to determine the occurrence of memory effects during general anaesthesia. In the following paragraphs a number of relevant theoretical, practical, and methodological aspects are discussed on the basis of the studies described in this article.

Depth of anaesthesia

To begin with, a crucial theoretical issue in research into memory for intraoperatively presented material is the lack of an uniform, objective measure of 'depth' or 'adequacy' of anaesthesia[66]. Thornton, Konieczko, Jones, Jordan, Doré, and Heneghan[67] described 'depth of anaesthesia' as: "...a state of the central nervous system resulting from a balance between the depression caused by anaesthetic drugs and arousal caused by surgical or other stimuli" (pp. 372-373). No matter how adequate a certain anaesthetic technique may seem, it is very difficult to determine if a surgical patient was 'unconscious' for the entire duration of the operation even when adequately anaesthetized by accepted criteria. The clinical signs (such as changes in pupil size, blood pressure, heart rate, sweating, and tears) that are used to assess adequacy of anaesthesia only assess activity of the autonomous nervous system, and not cognitive function[10].

Consequently, the most worrying problem is that instances of conscious perception ('awareness') during general anaesthesia are very difficult to detect and may go unnoted[68]. Furthermore, with regard to research into unconscious memory for intraoperative events: the occurrence of unconscious information processing can always be attributed, theoretically, to a temporarily light anaesthesia. In order to find convincing evidence of unconscious memory for intraoperative events, attention should be paid in each new study to the best possible assessment of anaesthetic adequacy. We distinguish two different approaches to the problem:

The physiological approach:

Auditory information processing during anaesthesia, i.e., the actual physiological route from incoming stimuli to electrical stimulation of the cortex, can be assessed directly by means of Auditory Evoked Potentials (AEPs). AEPs are the electrophysiological responses of the central nervous system to auditory (sensory) stimulation (e.g., the presentation of clicks). These responses can be subdivided into three parts: the brainstem response (which is obtained in the first 15 ms after stimulation); the early cortical response or midlatency cortical response (from 15 to 80 ms); and the late cortical response (from 80 to 1000 ms). Studies into the applicability of AEPs in measuring anaesthetic depth have concentrated on the effects of different anaesthetics on these three components of the Auditory Evoked Response (AER). For instance, Thornton and colleagues[67] demonstrated graded changes with increasing anaesthetic drug concentrations (six different anaesthetics) in the early cortical response during surgical stimulation. Schwender and colleagues[63] found that when early cortical responses were preserved, auditory information information was processed and remembered postoperatively. Munglani, Andrade, Sapsford, Baddeley, and Jones[69] demonstrated a correlation between changes in AEPs and changes in explicit memory at low doses of anaesthesia, with and without surgical stimulation. Their work, and the work by Thornton et al. and Schwender and colleagues shows that AEPs can be used to show the graded effects on the brain of different anaesthetics and, even more important, indicate the point where the physiological parameters indicating intraoperative perception and possibly also memory are suppressed by anaesthesia. Thornton[70] described a number of requirements the AEP should meet in order to be an instrument to assess anaesthetic depth. The AEP should a) show graded changes with anaesthetic concentration; b) show similar changes for different agents; c) show appropriate changes for different agents; and d) indicate awareness or very light anaesthesia. At this moment requirements a), b), and c) have been satisfied, and we believe that AEPs have the potential to meet d) in the near future[69,71].

The psychological approach:

As long as evidence for memory during anaesthesia can theoretically be interpreted as due to a temporarily lightened state of anaesthesia, it is difficult to make any judgements about its nature (conscious or unconscious?). Some form of unconscious perception may take place during anaesthesia[72], whereas on the other hand patients' memory for intraoperative material could be based on conscious perception with subsequent amnesia.

To find out if any effects found can be interpreted as purely unconscious, any conscious recollections to the intraoperative period need to be 'excluded' from postoperative memory performance. The Process Dissociation Procedure (PDP) developed by Jacoby and his colleagues[58,73,74], is based on the assumption that memory test performance is mediated in part by conscious processes and in part by unconscious processes. PDP provides a tool for investigating the extent to which performance on a memory test is mediated by consciously controlled versus unconscious memory processes. In other words, it is a method to distinguish between conscious and unconscious contributions to postoperative memory performance. To illustrate the procedure, a standard PDP-experiment is conducted as follows: subjects are presented with words and later tested with word stems (e.g., pension; pen---). For word stem completion subjects are instructed to complete word stems with words that were not presented earlier (*exclusion condition*). The instruction accompanying the *inclusion condition* is to complete word stems with words subjects recall or, if they cannot do so, with the first word that comes to mind. If memory for the words is perfect subjects will always complete stems with old words in the inclusion test and with new words in the exclusion test. In other words, responding would be under complete intentional or conscious control. A patient who was anaesthetized on the other hand, is supposed to be unable to consciously recollect the intraoperative period. As a consequence, he or she would show (complete) lack of intentional control by being as likely to respond with an old word when trying not to (exclusion condition) as when trying to (inclusion condition). If performance is also mediated by *intentional* processes based on conscious perception during anaesthesia, old words will be suppressed on the exclusion task and reproduced on the inclusion task. In other words, conscious processes are demonstrated if and when subjects can follow the inclusion and exclusion instructions. Likewise, automatic or unconscious processes are demonstrated if and when subjects fail to follow the instructions.

Jacoby and his colleagues have applied the PDP successfully in a large number of experiments to separate and measure controlled (conscious) and automatic (unconscious) processes underlying task performance[58,73-75]. In our view, PDP could be helpful in anaesthesia studies to assess the extent to which performance on postoperative memory tasks is mediated by either conscious or unconscious processes, or a combination of both.

Application of this technique would provide insight into the effects of anaesthetics on consciousness, given that memory for intraoperative information exists. An important prerequisite for the application of PDP is the assumption that anaesthetized patients do perceive and process information during surgery. If there is no perception and subsequently no memory, PDP will obviously not yield any additional information about how conscious or unconscious memory for intraoperative material is. For this reason it is too early to propagate PDP as a successful tool in anaesthesia studies. Although there is more evidence of memory in anaesthesia than a few years ago[3], more replications of positive findings are needed[65]. Subsequently, the feasibility and applicability of PDP designs in anaesthesia studies and in surgical patients needs to be tested. Graf and Komatsu[76] have pointed out the practical and theoretical difficulties associated with PDP. For instance, the complexity of the instructions required for the procedure make PDP less suitable for use in patients with certain forms of brain damage. So far, one study has been conducted in which a component of the PDP procedure was applied. Bonebakker, Bonke, Klein, Wolters, Stijnen, Passchier, and Merikle[77] (submitted, see Chapter 4) tested surgical patients with stem completion under exclusion instructions. Patients had been presented before and during general anaesthesia with common words. Shortly after surgery and 24 h later, they were instructed to complete word stems with the first word that came to mind but <u>not</u> with words they remembered having heard earlier (exclusion instructions). Patients appeared to be unable to exclude the intraoperative words, which was considered an indication of unconscious memory. Exclusion of preoperatively presented words was, as expected, more successful although patients did not exclude all the preoperatively presented words.

Anaesthetic mixture

In everyday medical practice a great variety of anaesthetic techniques and cocktails is employed. Until recently it was more or less clear that evidence for memory and conscious perception ('awareness') in general anaesthesia was especially found in studies in which nitrous oxide with or without an opioid had been employed (e.g., Bethune et al.[43], Jelicic et al.[54], Schwender et al.[63], see also Utting[78]). This technique entails the administration of nitrous oxide in oxygen, in combination with a neuromuscular relaxant, with or without supplementary opioids and is considered to act on specific parts of the brain. However, evidence for memory has also been found with techniques in which volatile agents (i.e., halothane, enflurane, isoflurane) were used in addition to nitrous oxide[50,53,62,77]. The volatile agents are considered to suppress cognitive functions more effectively than nitrous oxide in oxygen with or without opioids[9]. In conclusion, the exact effect of anaesthetic mixture on memory during anaesthesia is unclear. The only solution would seem the best possible assessment of anaesthetic depth in each experiment as long as there is no way to standardize the anaesthetic state of the brain.

More can be said about the role of benzodiazepines with regard to studies into memory in anaesthesia. Benzodiazepines are used in common anaesthetic practice as preoperative sedatives or intraoperative anaesthetics and are known to have amnesic properties that affect conscious memory. Ghoneim and Mewaldt[79], in an interesting review on benzodiazepines and memory, classified commonly employed memory tasks into categories based on their sensitivities to the effects of benzodiazepines. They concluded that mainly direct tasks of memory are sensitive to benzodiazepines (see also Polster, McCarthy, O'Sullivan, Gray, and Park[80]). Furthermore, memory for information learned prior to the administration of the drug is not impaired by benzodiazepines.

However, indirect memory tasks were not included in this classification and it is difficult to determine the exact effects of benzodiazepines on memory *during* anaesthesia on the basis of anaesthesia studies with indirect tasks. There is evidence that unconscious memory processes are spared after benzodiazepine administration[81], although the majority of investigators have found negative results with benzodiazepines affecting performance on indirect memory tasks[52,61,82,83].

Individual sensitivity

Patients can differ in their sensitivity to information presented during anaesthesia. Millar[33,84] in particular has called attention to individual variation being a relatively neglected factor in anaesthesia research. By comparing the data of two suggestion studies[32,34] Millar demonstrated that group means and standard deviations may easily mask such inter-individual differences because effects can be caused by the extreme reactions of a minority of subjects. This is further illustrated by the results from the behavioural-suggestion studies by Bennett et al.[22] and Goldmann et al.[48] in which the entire effect was caused by the performance of two and four patients, respectively, in samples of 11 and 21 patients. In order to determine the role of individual variation, Millar[84] advocates the presentation of outcome in scatterplots and the use of larger samples. The critical role of sample size is further supported by the implicit memory research; small effect sizes and a large number of false positives are characteristic of all studies of implicit memory *and* anaesthesia. It is therefore clear that large samples should be used and effects should be studied per patient.

Differences between patients in their anaesthetic state and the impact and location of the surgical procedure are also important. The latter factor can be corrected, but as pointed out earlier, variations in the state of anaesthesia cannot be detected easily (see also the paragraph on depth of anaesthesia). This type of research needs a 'gold standard' of depth of anaesthesia.

Choice of stimuli

An issue that has clearly not been addressed satisfactorily in most studies with single words as stimulus material, is the selection of suitable words. Most investigators have selected their stimuli from 25 to 30 years old norms like the Palermo and Jenkins Word-Association Norms[85], the Kucera and Francis norms[86], and the Battig and Montague Category Norms[87] (e.g., Westmoreland et al.[52], Brown et al.[56], Kihlstrom et al.[62], Parker et al.[83]). Everyday-language changes rapidly in the modern world, and populations under study may not always be representative of the entire population with regard to verbal capacities or habits. Therefore, it would be better if experiments were preceded by a pilot-study into the idiosyncratic reactions and responses of a representative sample of subjects (for instance, surgical patients from the same hospital as where the experiment is going to take place). As an illustration: when the Category Generation Task is employed, adequate norms are very important. Cueing subjects with category names (e.g., 'colours') may trigger strongly encoded, pre-experimental associations of typical exemplars (e.g., 'red') to the target categories (see also: Slamecka[88], and Lovelace[89]) instead of the experimental words (e.g., 'orange'). Two recent studies demonstrated that low-frequent category exemplars do not result in memory effects[50,55], whereas more frequent exemplars apparently do[53,54].

Another argument in favour of selecting suitable norms in advance is the vocabulary of surgical patients who have just woken up from general anaesthesia. In most studies, memory is tested shortly after anaesthesia at a moment when patients are often very sleepy, in pain, and nauseous. This physical condition may affect consciousness and, as a consequence, affect patients' vocabulary in the sense that they may respond differently, in comparison with other circumstances.

Type of stimuli and task

In memory research a distinction is made between *perceptual* and *conceptual* tasks of memory[90,91]. Perceptual memory tasks appeal to the physical properties of stimuli (e.g., whether a word begins with the letters STA--). Performance on these tasks is determined by the resemblance between stimulus material presented during learning-phase and test-phase. Conceptual tasks of memory appeal to the meaning of a stimulus. Performance on these tasks requires the analysis of the meaning of the stimuli presented during the learning-phase (e.g., "When did Queen Beatrix come to the throne?").

Millar[64] and Ghoneim and Block[65] suggest that patients who have been anaesthetized perform better on perceptual tasks than on conceptual tasks. This conclusion is in accordance with the results reviewed in this article (see also Kihlstrom and Schacter[92], and Greenwald[72]). In addition, the relative familiarity of stimuli (common as compared to less common material) seems to determine normal performance on conceptual tasks[9,55]. Two experiments by Roorda-Hrdlicková and colleagues[53] and Bonebakker et al.[55] illustrate this assumption. More or less high-prototypical words (e.g., 'banana' for FRUIT) were reproduced postoperatively, whereas low-prototypical words (e.g., 'cod' for FISH) did not cause an effect, with the same anaesthetic technique and conceptual memory task in both experiments. It is important to mention the role of the anaesthetic mixture in this context. The studies by Jelicic and colleagues[59] with the 'general-knowledge' task and Schwender et al.[63] with the Robinson Crusoe-story demonstrate that conceptual information *can* be processed during anaesthesia without volatile agents. With regard to anaesthesia studies, it would be interesting if these experiments were replicated or if the meaning and/or familiarity of experimental stimuli was deliberately manipulated in order to find out what the exact roles of type of stimuli in combination with memory task are.

Intraoperative stimulus presentation

Where the intraoperative period is concerned, investigators follow various procedures. In some experiments stimuli are presented either shortly after induction of anaesthesia and before the first incision (e.g., Brown et al.[56]), or at the end of the surgical procedure (e.g., Bennett et al.[22]; Goldmann et al.[48]). In both these situations stimuli are presented during periods that do not reflect a steady, adequate anaesthetic state; the period between induction and the first skin incision is a transitional phase during which the narcotic effects of sedative drugs administered at induction are gradually taken over by the effects of volatile anaesthetics or other anaesthetics for maintenance. Likewise, the period after wound closure is not representative of adequate anaesthesia either, because by that time additional doses of anaesthetics are no longer administered. As a consequence anaesthesia becomes less 'deep' and eventually the patient wakes up. Memory for material presented during the latter period may reflect conscious rather than unconscious memory. If one wants to find evidence for perception during *adequate anaesthesia*, one should present stimuli during a period that represents a steady anaesthetic state with surgical stimulation, i.e., a situation that can be generalized to the reality of common surgical practice.

In some studies, patients were not prevented from hearing operating theatre sounds before or after stimulus presentation because either the earphones were removed, or no filler sounds were presented for the remainder of the operation. It is conceivable that words or sounds perceived by patients may interfere with the critical stimuli during subsequent memory test. To illustrate this point, patients in the study by Brown and colleagues[56] (see *indirect memory tasks*) were presented with words shortly after induction and before the first incision. After this *2 min* presentation, the headphones were removed for the rest of the operation. Apart from the possibility of interference from other sounds, the critical stimuli were presented at a moment that did not reflect an adequate anaesthetic state with surgical stimulation (see also Eich et al., 1985).

An additional issue is the number of stimulus presentations necessary to result in memory effects. Two studies described in the paragraph *indirect memory tests* addressed the effect of number of presentations[55,56], but neither yielded clear results. Block et al.[50]

found that nonsense words that had been presented frequently (at maximum 16 times) were preferred more on a postoperative preference task than words that had been played less frequently during anaesthesia, but this was not replicated in additional control tests. Winograd, Sebel, Goldman, and Clifton[94] varied the number of presentations of fragments of ethnic music. Their patients were exposed 0, 3, or 12 times to musical stimuli during general anaesthesia. Postoperatively there was no relationship between number of intraoperative exposures and implicit preference ratings either.

In most anaesthesia studies, multiple presentations of stimuli have been employed, and it is not yet clear if one presentation is sufficient to cause a memory effect. From a methodological point of view it is advisable to standardize the moment of presentation and its duration, so that results can easily be compared.

In summary, the following aspects have to be considered with regard to the intraoperative procedure: a) presentation of a neutral filler sound before and after stimulus presentation; b) stimulus presentation during a 'steady anaesthetic state' at a fixed moment in time, relative to the beginning or end of the procedure; c) standardized length of stimulus presentations[95].

Postoperative measurement

Another issue that needs to be considered is the nature and moment of postoperative tests or measurements. Again, there is little uniformity in this respect. For instance, what characterizes therapeutic-suggestion studies is the postoperative measurement of concepts that are very difficult to assess objectively, like postoperative recovery and subjective well-being. These outcome variables are assessed by means of different questionnaires and often the days to discharge from hospital are taken as an indication of postoperative recovery. Consequently, findings are difficult to interpret because these types of measurements are often subjective and determined by many other factors (length of hospital stay can, for instance, depend on the policy of a particular hospital). An exception to this 'rule' is the assessment of postoperative analgesic requirements measured by means of Patient Controlled Analgesia (PCA) as studied by the research groups of Steinberg et al.[39], McLintock et al.[40], and Caseley-Rondi et al.[41]. The amount of pain medication a patient requires is a relatively objective measure if one corrects for the relative impact of the surgical procedure and for interindividual differences in how patients experience pain[96].

With regard to postoperative memory tests, a number of other aspects need to be considered. First, similar to the nature of the information presented during anaesthesia, postoperative tests must not be too complex because they have to appeal to the perceptual level of information-processing. Perceptual information-processing requires less cognitive effort at the time of encoding than conceptual priming[65]. Secondly, learning phase and test phase have to be matched with respect to sensory modality (both auditory) and to the voice in which the stimuli are presented. Research in conscious subjects has demonstrated that implicit memory processes are extremely sensitive to changes in modality and voice[97], but the exact role of these latter two factors in anaesthesia-experiments needs to be tested. Finally, the delay between learning phase and test phase must not be too long. On the basis of several negative findings, we have argued that implicit memory during anaesthesia is an elusive, transient phenomenon[55]. There are some recent findings indicating that these effects may last longer than the first 24 h after surgery[63,77], but then again, the duration of postoperative memory effects needs to be studied more extensively. Until then, valuable information may be missed if the interval between stimulus presentation and postoperative testing is too long.

The experimental possibilities seem limited and evidence for memory and perception in general anaesthesia is very difficult to interpret because there is as yet no instrument to assess depth or adequacy of anaesthesia. As long as this situation continues to exist positive findings can always be attributed to temporarily 'light' anaesthesia. Given the described experimental restrictions, the boundaries of what can be investigated will eventually be reached. However, the present research would certainly gain in clarity and quality if more uniformity in experimental methods and procedures were pursued and more results replicated.

Concluding remarks

The research area we have reviewed in this article is part of a much larger area in which the effects of unconscious processes on psychological functioning are studied. As described under *Unconscious processes*, there is a long-standing tradition of research into unconscious perception and the studies into memory and perception in anaesthesia can be regarded in this context. General anaesthesia can be considered a specific manipulation of consciousness. Subjects lack conscious recollections of what happened during the intraoperative period because they were not aware of what happened. This absence of conscious experiences allows researchers to assess unconscious activity, and results from such studies can make important contributions to theories of unconscious information-processing.

There are other ways to study unconscious processes. A frequently used laboratory manipulation is masking of stimuli (i.e., a very short presentation of a stimulus followed by an irregular mask that disrupts the afterimage) so that the stimuli cannot be consciously recognized but still affect subsequent task performance[72,98]. An illustrative example of this approach is an experiment by Murphy and Zajonc[99]. Photographs of faces with either angry or happy expressions were presented very briefly, prior to the presentation of a neutral, unfamiliar stimulus (a Chinese character). During a subsequent 'two-alternative-forced-choice' task, subjects were unable to tell which face had been presented in the short presentation condition. Nevertheless, the expression of the face strongly influenced the attractiveness of the Chinese character compared to a control condition. This effect was absent when faces were presented longer, that is, consciously perceived. This finding indicates that consciousness may inhibit the processing of stimuli with an 'emotional' meaning[100]. In analogy with this assumption is the possibility that during anaesthesia such inhibitory influences are suppressed, thus undermining patients' ability to resist adverse emotional effects of surgery.

Opposite to the absence of conscious perception during anaesthesia or during masking tasks is the situation in which stimuli are consciously perceived under full attention, but nevertheless not consciously connected with each other. To illustrate: Lewicki, Hill, and Czyzewska[101] presented subjects with slides of women's faces, either with long or short hair. Each presentation was accompanied by a description of that particular woman, in terms of intelligence or friendliness; all short-haired women were very kind, and all long-haired women were very intelligent, or vice versa ('hidden covariation'). Subsequently, slides of other women's faces were presented and subjects were asked to describe each face in terms of intelligence or friendliness. When a slide of a long-haired woman was presented and subjects were asked if this woman was intelligent, the majority of subjects agreed and response latencies were longer. If the same question was asked about a short-haired woman, subjects tended to disagree. In an earlier phase of the experiment, a connection had been made between long hair and intelligence leading to this particular performance during the test-phase of the experiment. Lewicki explicitly asked his subjects if there was a connection between hair-style and personality. The finding that none of the subjects found that there was such a connection indicates unconscious information-processing.

Although studies into the effects of intraoperative positive suggestions on postoperative well-being have yielded inconsistent results, results from laboratory studies that use other manipulations than anaesthesia[99,100,101] suggest that 'affective processing' is stronger in unconscious than in conscious states. Therefore, the possibility that incoming affective stimuli can harm surgical patients[102,103] is a matter that has to be considered carefully by everyone involved in anaesthetic and surgical care. As long as we do not know the psychological effects of overheard stimuli, we have to respect the potential vulnerability of surgical patients. Therefore, we want to stress the importance of research into memory and perception in general anaesthesia. More knowledge about this subject can definitely improve surgical care. Surgery itself is a major traumatic life event[102,104] with sometimes detrimental effects on cognitive functioning in later life[103]. Anaesthesiologists may use the results of this particular type of research for the prevention of 'awareness', the improvement of anaesthetic care and techniques, for promoting recovery, and for opposing adverse after-effects of surgery.

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Outline of the thesis

In the previous chapter (Chapter 1) a review of the literature on memory in general anaesthesia was given and several practical and methodological aspects were discussed. It was concluded that more uniformity in experimental designs and procedures should be pursued and that investigators should concentrate on determining the exact circumstances under which memory effects in anaesthesia occur. The central issue of the present project is the determination of some of these experimental conditions. As discussed in Chapter 1, a number of experimental conditions are likely to determine the occurrence of an effect. The specific experimental parameters we concentrated on in the following three experiments were the *number of stimulus presentations*, the *nature of the stimuli and tasks*, and the *interval between presentation of stimuli and postoperative memory test*. Each of these 'stimulus-characteristics' was manipulated within one experiment. In all three experiments a similar, standardized anaesthetic technique was employed and comparable subject populations were studied.

In the first study (Chapter 3) the effect of number of word presentations was studied by presenting specimens of familiar word categories (e.g., 'fruit', 'animals', 'musical instruments') a different number of times during anaesthesia. This study was based on two comparable experiments by our group in which memory for common category specimens was successfully demonstrated[1,2]. In contrast with these studies, less common specimens and different word categories were employed.

In the second study (Chapter 4) we specifically manipulated the familiarity of words and used two different memory tasks. For reasons described in Chapter 1 (see *Choice of stimuli*), prior to this study, we collected words among representative surgical patients. In order to assess the duration of possible memory effects, patients were tested at two delays; i.e., 4 h (word completion) and 24 h (word completion and forced-choice 'yes/no' recognition) postoperatively. A method derived from cognitive psychology[3,4] i.e., the *exclusion task*, was employed to distinguish between conscious and unconscious contributions to postoperative word-completion performance (see Chapter 1, *Depth of anaesthesia*). In short, this task was used as follows: as an extra instruction to the word completion task patients were asked to exclude words they remembered having heard earlier during the experiment. The assumption underlying this procedure is that patients will be unable to remember the words presented during anaesthesia and consequently fail to exclude these words during the memory task. Such failure to exclude intraoperatively presented words (and the presence of a memory effect) would indicate unconscious memory. On the other hand, exclusion of the intraoperative words would indicate the absence of a memory effect or some amount of conscious memory for the stimuli.

The main objective of Study 3 (Chapter 5) was to replicate Study 2. Given the number of negative findings in this field of research, replicable results are required[5-7]. The second objective of this study, like in Study 1, was to assess the effect of number of presentations on postoperative memory performance. During anaesthesia patients were presented with both one and multiple presentations of words. Postoperatively, memory was tested by means of word completion and forced-choice 'yes/no' recognition. For reasons described in the previous paragraph, exclusion instructions accompanied the word-completion task.

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CHAPTER 3

Implicit memory during balanced anaesthesia: lack of evidence

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Abstract

The effect of number of presentations on implicit memory for words was studied in anaesthetized patients. During standardized, balanced anaesthesia, 81 surgical patients were presented with less common specimens of familiar word categories. For each of 3 word categories the number of word presentations varied between the patients (0 (control), 5, or 30 presentations). Postoperatively repetition priming was tested by asking patients to generate exemplars for each of the word categories. No implicit memory for the words presented during anaesthesia was found and consequently no effect of number of word presentations could be demonstrated. It is suggested that this finding which contradicts prior results may be caused by the relatively low familiarity of the words used.

Introduction

Information processing during general anaesthesia may occur under some circumstances. Evidence from several studies into memory and learning during anaesthesia suggests that anaesthetized patients can somehow process, and later reproduce information that was presented during surgery[1-3]. This conclusion is based on tests measuring repetition priming effects, i.e., a facilitation of performance due to prior exposure to certain stimuli. These tests have been labelled implicit memory tests[4] because, unlike standard or explicit tests of memory, they do not require an explicit reference to a previous learning episode.

Recent studies reporting both positive[1,2] and negative[5] results of implicit memory during anaesthesia raise the issue under what conditions the effect will occur. Factors that may be involved are, for example, the number (or intensity) of presentations of stimuli, the nature of the implicit memory task, and the anaesthetic technique that is used.

Two of these factors are put to test in the study reported here, i.e., the number of presentations and the nature of the stimuli.

The number of stimulus presentations necessary to cause a priming effect is unknown. On the basis of several studies[5,7-9], Ghoneim and Block[6] have suggested that number of stimulus presentations may affect implicit memory performance[10,11]; the more stimulus presentations a subject is exposed to, the more likely priming will occur. The recent experiments conducted by our group[1,2] have demonstrated clear effects after 30 presentations. We hypothesized that variation of stimulus-intensity causes variation in priming effects.

Whether patients can reproduce postoperatively verbal information presented during anaesthesia also seems to depend on the familiarity of the stimulus material. Roorda-Hrdlicková, Wolters, Bonke and Phaf[1] and Jelicic, Bonke and Appelboom[2] found clear priming effects in anaesthetized patients. In both studies a category exemplar generation task was used and familiar exemplars of common categories were presented as stimuli during balanced anaesthesia. Block, Ghoneim, Sum Ping and Ali[5] however, failed to demonstrate priming using the word category production task during two types of general anaesthesia (nitrous oxide and opioids, and nitrous oxide and isoflurane). Contrary to Roorda-Hrdlickovà et al.[1] and Jelicic et al.[2], Block et al.[5] employed somewhat unusual or difficult categories, e.g., 'type of wood', 'type of male clothing', for which it may be more difficult to generate exemplars (see also Ghoneim and Block[6]) than for more common categories.

In the present study, these issues were put to test. On the basis of results of earlier studies[1,2,5] we hypothesised that less familiar exemplars of common categories might also result in priming effects during general anaesthesia. (Results from studies into priming in amnesic and normal subjects even show that less familiar words result in larger priming effects). So, less familiar exemplars of common word categories were used as target words, and were presented during balanced anaesthesia. Moreover, for each of the word categories the number of word presentations was varied between subjects in order to assess a possible effect of stimulus intensity.

Methods

Subjects

One-hundred-and-three patients were asked to participate in the experiment, four refused to take part. A total of 18 patients were excluded from the actual experiment: in seven cases the surgical procedures took less than 30 min, six patients had received benzodiazepines 30 min before surgery, two had hearing difficulties, one spoke Dutch poorly, one was too disoriented after surgery to answer any questions, and in one case an uncommon anaesthetic technique had been used.

Thus, 81 informed and consenting patients (ASA I or II) scheduled for elective surgical procedures under general anaesthesia with an expected duration of 45-240 min, participated in the experiment. They were 53 females (mean age 41.0 yr, range: 19-65) and 28 males (mean age 39.9 yr, range: 19-66) and met the following criteria: native speaker of Dutch, no serious hearing impairment, no alcohol- or psycho-active drug abuse, and no known psychiatric disorder. The study was approved by the local Medical Ethics Committee. Neurosurgery (peripheral) was performed in 32% of the patients (13 women, 13 men), gynaecological surgery in 20% (16 women), general surgery in 17% (11 women, 3 men), orthopaedic, urological, trauma, or dental surgery in 17% (5 women, 9 men), and plastic or reconstructive surgery in 14% (8 women, 3 men).

Materials

Six target words were selected from a set of word category exemplars for which spontaneous generation frequencies had been determined as follows. In a pilot study, 83 subjects (staying in the same hospital as those who later participated in the experiment) were asked to name the first four examples that came to mind for each of 11 categories. For the actual study, words with a relatively low spontaneous generation frequency (frequency of occurrence ranging from 10 to 17 per cent) were selected in order to minimise the possibility of false positives. With regard to the word categories, we chose categories for which the total numbers of different exemplars were comparable (range: 34-47 exemplars). *Musical instruments*, *birds*, and *fish* were selected as categories, and *clarinet, saxophone, pigeon, gull, cod*, and *salmon* as the respective target words. The words were tape-recorded onto three audio-tapes as follows. On each tape a different combination of four target words (i.e., from two different word categories) was recorded (e.g., 'pigeon-gull' and 'cod-salmon'). The two remaining words of the third category (e.g., 'clarinet' and 'saxophone') were to serve as a control condition in the test phase. All tapes contained a 30-min presentation of the target words in the female voice of the experimenter. The target words were presented in pairs (i.e., *clarinet-saxophone, pigeon-gull*, and *cod-salmon*) and recorded at a speed of one word every 1.5 s, introduced by: "Please, listen carefully...". On all three tapes each pair of target words was either presented 0 (the control condition), 5, or 30 times with an interval between presentation of each series of 40 s. The intervals were filled with a neutral sound.

The three tapes were visually identical and had been coded A, B, and C by someone not involved in the experiment. Not until all data were collected were the codes broken.

Procedure

On the afternoon before surgery, each patient completed the state version of the State-Trait Anxiety Inventory[12] to assess preoperative anxiety. All patients underwent the following standardized, balanced anaesthesia:

If required, diazepam 0.1 mg/kg (14 patients (17%)), temazepam 10 mg (3 patients (4%)), or oxazepam 10 mg (2 patients (2%)) was given orally the night before surgery. Premedication was with atropine 0.5 mg, intra-muscularly, 30 min before the operation.

Induction: sufentanil 0.5-μg/kg, vecuronium (0.1 mg/kg), and thiopentone (4 mg/kg). Maintenance: nitrous oxide in oxygen 2:1, and isoflurane 0.25-0.5 vol%, continuous end-tidal concentration of 0.2-0.4 MAC; incremental doses of sufentanil and vecuronium where administered when needed. The lungs were mechanically ventilated. At the end of the operation, prostigmine combined with atropine was given for reversal of residual muscular relaxation.

Patients were randomly (by means of a random list) assigned to one of the three cassette tapes in a double-blind fashion: tape A (29 patients; mean age 42.1 yr), tape B (20 patients; mean age 38.8 yr), and tape C (32 patients; mean age 39.2 yr), stratified over three age groups (18-35, 36-50, and > 50 yr) and three levels of expected pain stimulation during surgery (based on the location of surgery and the relative impact and intensity of the operation). All judgements were made by the attending anaesthetists and were based on their knowledge and experience.

From about 15 min after the induction, all patients were played the neutral (bird) sounds via headphones, using a Sony WM-EX 70 walkman. Five minutes after skin incision, the appropriate tape (A, B, or C) was started. After 30 min, bird sounds were again played to all patients for the rest of the operation.

The postoperative interview took place within 3 hr after surgery. One patient, however, refused to cooperate one hour after surgery but was tested 2 hr later. The mean interval between the beginning of presentation of target words during surgery and postoperative interview was 115 min (range: 60-300 min). Patients were interviewed about any explicit recall of intraoperative events, with the following questions: "What is the last thing you remember before you were put asleep for your operation?", "Did you hear anything during the operation?", and "Did your dream anything during the operation?". Then patients were asked to name the first three specimens that came to mind for the categories 'musical instruments', 'birds', and 'fish'. When target words were generated, these were scored as 'hits'. A maximum of six hits could thus be obtained.

For each word category, the number of hits were compared between the three presentation conditions (0, 5, and 30 presentations) using Jonckheere-Terpstra's test[13]. This test is sensitive to an increase in outcomes (number of hits) when groups are compared which have a natural order, i.e., an increase in the number of word presentations.

$P=0.05$ (two-sided) was considered the limit of statistical significance.

Results

Explicit memory

All patients remembered the i.v. administration of the anaesthetics for induction, whereas none had any recall of intraoperative events.

Implicit memory

There was a low incidence of hits in all three presentation conditions: 15 patients in the 0 presentations (control) condition (18%), 18 patients in the 5 presentations-condition (22%), and 23 patients in the 30 presentations-condition (28%). The number of targets generated for each word category and for all three numbers of presentations (zero presentations in the control condition) are shown in table 1. Although there seems to be a small tendency that the number of targets increases with the number of presentations, this tendency is not significant as is shown in a Chi-square test on the total number of targets in each presentation condition (Chi-squared=1.69, n.s.).

Therefore, no implicit memory effect of presentation of the target words during anaesthesia was demonstrated.

Table 1 Number of patients (percentage) with respect to number of hits and number of word presentations for each word category.

		Word presentations		
Word categories	*Number of hits*	0 x	5 x	30 x
Musical instr.	1*	3 (10%)	4 (25%)	8 (25%)
	0	26 (90%)	16 (75%)	24 (75%)
	Total	29	20	32
Birds	2	1 (3%)	2 (7%)	0 (0%)
	1	9 (28%)	5 (17%)	10 (50%)
	0	22 (69%)	22 (76%)	10 (50%)
	Total	32	29	20
Fish	2	0 (0%)	2 (6%)	1 (3%)
	1	2 (10%)	5 (16%)	4 (14%)
	0	18 (90%)	25 (78%)	24 (83%)
	Total	20	32	29

P-values: 0.18 (Musical instr.), 0.32 (Birds), and 0.64 (Fish). * No patient scored 2 hits in the category *Musical Instruments.*

There was no relation between hit-scores and preoperative anxiety or estimated pain-intensity. The same applied to age and gender.

Discussion

Information-processing during anaesthesia was not detectable under the circumstances we created. Presentation of less common category specimens during balanced anaesthesia did not yield a clear implicit memory effect. No more than a slight, nonsignificant tendency for some of the words could be detected. As a consequence, no effect of number of word presentations was demonstrable, and the hypothesis that implicit memory depends on the number of presentations could not be supported.

These findings are not in accordance with earlier studies by our group[1,2]. Yet most conditions in this study were similar to the previous studies (i.e., type of task, presentation-test delay, anaesthetic technique, and, at least in one condition, the number of presentations). The only obvious difference between the present and prior studies is in the nature of the stimuli used. In this study less common specimens of categories were used. Similar stimuli were used in the study of Block et al.[5], who also did not find a priming effect (it has to be noted however, that in that study a different anaesthetic technique was used in addition). We conclude that the use of less common exemplars accounts for the failure to demonstrate priming effects. Any possible priming effect may have been swamped by the pre-experimental strength of associations of typical exemplars to the target categories. It has been shown by Slamecka[14] for example, that the acquisition of 'new' associations to a certain stimulus does not easily produce 'unlearning of strong pre-experimental associations to this stimulus.

This effect may have been aggravated because the categories used in this study contained a large number of possible exemplars (range 35-47 specimens). Raising the strength of two relatively less common exemplars may have been insufficient to reliably increase the probability that they are generated when three exemplars have to be named spontaneously. Post-hoc comparisons revealed that there were no differences between the pilot and the experimental study in the frequencies of occurrence of the most typical category exemplars. Again, this is an argument for the assumption that the effect of presenting less common exemplars during anaesthesia is not sufficient to overcome strongly ingrained, pre-existing associations between categories and category-specimens. In order to avoid these effects of prototypic specimens of categories, subjects probably should have been required to name a number (at least three or more) of examples of each category. By doing so, an effect of intraoperative presentation of category exemplars on implicit memory might emerge.

An alternative, though somewhat related, explanation for the present findings is that the implicit memory task we used is less suitable for finding priming in general anaesthesia. Presenting category exemplars and later cueing these exemplars with their category labels is known as *conceptual* priming (i.e. priming a relatively high level of stimulus analysis). Kihlstrom and Schacter[15], and Millar[16] have suggested that conceptual priming may require more information-processing capacity than is available to adequately anaesthetized patients. Due to the suppressing effects of anaesthetics on information processing functions of the brain, it is possible that words with a relatively low familiarity are not sufficiently activated to induce strengthening of associations. This explanation may account for the discrepancy between findings in studies into priming in other populations (amnesic and normal subjects) and the present study with regard to the effect of familiarity of the target words. In these other populations, the presentation of less familiar words has resulted in larger priming effects. Actually, this was one of the reasons why we chose target words with low familiarity in the present study. However, the relative frequency of stimuli seems to have an other effect on implicit memory in anaesthetized subjects than in amnesic or normal subjects.

Doubt remains whether implicit memory for intraoperative events is more than an elusive, possibly even spurious, concept[17-20]. Therefore, future studies will have to assess the exact conditions in which repetition priming occurs, and attempt to bring the phenomenon under experimental control. On the basis of the outcome of this study, we suggest that such studies into implicit memory in anaesthesia should first concentrate on stimulus characteristics (e.g., type of material and number of presentations) and on the optimal type of task (e.g., conceptual or perceptual priming) required to obtain repetition priming. In a next stage the effects of delay between presentation and test, and of anaesthetic procedures and anaesthetic depth on the occurrence of implicit memory might be established.

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CHAPTER 4

Information-processing during balanced anaesthesia: evidence for unconscious memory.

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Abstract

Memory for words presented during general anaesthesia was studied in surgical patients undergoing elective procedures under balanced anaesthesia. Before and during surgery, 80 patients were presented with both common and less common words via headphones. At the earliest convenient time after surgery (within 4 h) and 24 h later, memory was tested by asking patients to complete verbally presented word stems with the first word that came to mind. Part of the word stems corresponded with the experimental words (target items). The remaining word stems served as control items (distractors). After the second word completion session (24 h after surgery) subjects were requested to perform a 'yes/no' forced-choice recognition task to assess recognition memory for both the pre- and intraoperative words. Memory for the words presented during anaesthesia was demonstrated immediately after surgery and 24 h later by means of both tasks. Word completion was better for common words, whereas recognition memory was apparent for both common and less common words.

Introduction

Over the past few years, perception and memory during general anaesthesia have become major scientific topics. Both anaesthesiologists and psychologists attempt to find out whether patients can perceive information presented during general anaesthesia, and if so, what the preconditions for such nonconscious cognition are. Some studies reported that under some circumstances anaesthetised patients can process information that was presented intraoperatively[1]. In other studies information-processing during general anaesthesia could not be demonstrated convincingly. The reason why these results are so different remains unclear. However, there is growing consensus[1] as to which experimental factors are likely to determine the occurrence of memory effects during general anaesthesia, i.e., anaesthetic technique, nature of the intraoperative stimuli, type of memory task, delay between stimulus presentation and memory test, and dissimilarity of sensory modality between learning phase and test phase.

An important starting-point of research into memory in general anaesthesia is the distinction between direct and indirect tasks. This classification of memory tasks is identical to a classification of tasks based on the distinction between explicit and implicit measures of memory[2]. However, the implicit/explicit terminology is used to classify both memory processes and memory tasks, thus implying that specific memory processes underly performance on specific memory tasks[3]. We prefer to make a distinction between memory processes and empirical measures, because it has become more and more clear that most measures of memory are affected by *both* conscious and unconscious memory processes[4-6]. The direct/indirect distinction is based on task instructions only and does not require assumptions about correlations between task performance and underlying memory processes[3]. In direct tasks, subjects are explicitly instructed to remember previously presented material, i.e., to discriminate 'old' from 'new' material. Examples of direct tasks are free recall and recognition. In indirect tasks, the instructions do not make any reference to previously presented material. Therefore, performance on these tasks may not involve conscious recollections of a previous learning episode. Examples of indirect tasks are word-stem completion[7] (subjects have to complete word stems, the first two or three letters of a word, with the first word that comes to mind) and category generation (subjects have to name the first examples that come to mind of familiar word categories, like 'peach' for 'fruit'). To date, memory for material presented during general anaesthesia is assessed mainly by means of indirect tasks in which the instructions do not make any reference to the material presented during surgery[1].

Closely related to the use of indirect tasks in anaesthesia studies is the issue of the exact nature of the stimulus material that is used. In memory research, it is well established that single, familiar words ('banana', 'house') require less cognitive processing before storage in memory takes place than more complex material. In anaesthetised patients, unconscious memory effects are more likely to occur when single, familiar stimuli are presented, that is, information that can be processed at a *perceptual* level. Assessing unconscious memory by presenting more complex material and using more complex tasks requires cognitive processing at a more *conceptual* level, which is a relatively high level of stimulus analysis[1,8,9]. Information-processing at a conceptual level may require more energetic processing capacity than is available to anaesthetized patients due to the suppressant effects of anaesthetics. Indeed, this was our experience in earlier studies into memory in general anaesthesia. Roorda-Hrdlicková, Wolters, Bonke, and Phaf[10], and Jelicic, Bonke, Wolters, and Phaf[11] found clear memory effects in anaesthetised patients after intraoperative presentation of familiar exemplars of common word-categories (e.g., 'banana' for 'fruit') and postoperative generation of word-category exemplars. Different anaesthetic techniques were used in these two studies. However, Block, Ghoneim, Sum Ping, and Ali[12], as well as Bonebakker, Bonke, Klein, Wolters, and Hop[13] found no memory effects using the same task, but with less common exemplars of word categories. Block et al.[12] used both category-generation and word-completion in their experiment and found evidence for memory during anaesthesia in word-completion but not in the word-category generation task. In view of these findings, it would be interesting to study the effect of presenting different types of words (e.g., common and less common words) on the occurrence of memory effects in a new experiment, using word-stem completion (perceptual processing). We reasoned that presenting anaesthetised patients with both common and less common words and later cueing them with word stems (the first two or three letters of words) might give us renewed access to memory in anaesthesia.

Since adequate general anaesthesia impairs conscious memory processes, it is logical to assume that intraoperatively presented material will not be recognized postoperatively. Indeed this is what some investigators who used traditional direct memory tasks like free recall and unforced recognition[14-17] have found. Caseley-Rondi, Merikle, and Bowers[18] recently found that their *forced-choice* recognition task showed sensitivity to information presented during general anaesthesia. We believe that if subjects are requested to respond to every item in the task, even if they are unsure, their answers may be based on unconsciously perceived material. In other words, (forced-choice) recognition tasks may reveal memory for information presented during general anaesthesia[12,18,19,20]. Thus, in the current study memory for words presented during surgery under general anaesthesia, is assessed by a direct task (forced-choice 'yes/no' recognition) as well as an indirect task (word-stem completion).

Unfortunately, a reliable measure of depth of anaesthesia is not yet available. Nevertheless, the recent work by Munglani, Andrade, Sapsford, Baddeley, and Jones[23] into the assessment of cognition during inhalation anaesthetia by means of particular aspects of the auditory evoked response, (the 'coherent frequency') is promising (see Chapter 1). No matter how adequate a certain anaesthetic technique may seem, there is still no reliable way to guarantee that all the patients in a particular study have in fact been anaesthetised completely for the entire duration of the operation. Consequently, evidence for memory for material presented during anaesthesia can always be attributed, theoretically, to a temporarily light anaesthesia. This makes it almost impossible to make any judgements about the nature (conscious or unconscious) of the memory effects found. In order to find out if any effects obtained in the context of general anaesthesia can be interpreted as purely unconscious, a measure of conscious experiences is needed. In a series of subliminal perception experiments, Merikle and Joordens[22] demonstrated that 'exclusion instructions'[4-6] can be used to distinguish between conscious and unconscious contributions to memory-task performance. The distinguishing characteristic of these instructions is that subjects are instructed *not* to use particular responses when performing a word-stem completion task. The rationale is as follows; if subjects can follow the exclusion instructions (i.e., if they are able to exclude particular responses), there is evidence for conscious control. In contrast, if subjects fail to follow the exclusion instructions (i.e., they still come up with particular responses), there is evidence for unconscious memory. In our present experiment the exclusion instructions were applied to both preoperative and intraoperative presentations of words. During postoperative word completion, patients were instructed to complete word stems with the first word that came to mind *except* the words that had been presented before and during anaesthesia. The critical hypothesis in our study was that patients would be able to exclude preoperatively presented words, which they would recall, but would fail to exclude words presented during anaesthesia of which they would have no conscious recall. Such an outcome would provide evidence for unconscious memory for the intraoperative words. In contrast, if patients perform either below or at baseline level on the intraoperative words, this would mean that they either have conscious memory or no memory at all, respectively, of material presented during anaesthesia.

A final issue is the duration of memory for material presented during anaesthesia. Effects were found when patients were tested immediately (within 3-5 h) after surgery[10,11] or as late as five days after surgery[23]. In the present study the issue of delay between presentation and test was put to test by administering tests after a short and a longer delay.

To summarize, the primary aim of our study was to investigate memory for words presented during general anaesthesia, using a standard, common anaesthetic technique and two different measures of memory. To find out if the effects that are obtained in this arrangement can be interpreted as purely unconscious, we used exclusion instructions in the postoperative word-completion task. The underlying assumption was that if patients were unable to follow the exclusion instructions and still came up with target words, there would be evidence for unconscious memory. We used both common and less common words as stimuli to be able to study possible effects of these two types of words. The duration of memory effects was studied by testing patients at two different moments, i.e., immediately after surgery and 24 h later.

Methods

Normative study

Before the experiment, normative material for the word-completion task was collected among representative surgical patients. We decided to collect this material among patients who had just undergone a surgical procedure under general anaesthesia, in order to arrive at a set of stimuli obtained under exactly the same circumstances as the actual experimental circumstances. After approval of the local medical ethics committee, forty-one informed and consenting patients (30 women and 11 men; mean age 37.2 yr, range: 18-60) were exposed to a neutral sound, via headphones, during surgery (mean duration of surgical procedures 53.7 min; range 10-270 min). Gynaecological surgery was performed in 46% (19 women), plastic or reconstructive surgery in 20% (5 women, 3 men), orthopaedic surgery in 15% (3 women, 3 men), trauma or general surgery in 12% (3 men, 2 women), and neurosurgery (peripheral) in 7% (2 men, one woman). Patients either received standardized, inhalational anaesthesia (32 patients, 78%) or intravenous anaesthesia (9 patients, 22%), depending on the type of surgery performed. All patients received atropine, 0.5 mg (i.m.) 30 min before surgery. Patients who required tranquillizers received midazolam 2.5-5.0 mg (i.m.) 30 min preoperatively (9 patients, 22%). Induction of inhalational anaesthesia was with sufentanil, 0.5 $\mu g.kg^{-1}$, vecuronium, 0.1 $mg.kg^{-1}$, thiopentone, 3-7 $mg.kg^{-1}$. Anaesthesia was maintained with N_2O/O_2 (2:1), isoflurane, 0.25-0.5 vol%, and sufentanil and vecuronium if required. Intravenous anaesthesia: induction with alfentanil, 0.5-1.0 mg, propofol, 2 mg/kg; maintenance was with propofol, 10, 8, and 6 mg/kg/hr, doses were adjusted every 30 min. If required, alfentanil 0.25-0.5 mg was given.

Within 1 to 24 h after surgery, 42 different word stems (the first two or three letters of selected words) were presented verbally to these patients, accompanied by the instruction to complete each word stem with the first word that came to mind. Thus, a set of spontaneous completion frequencies for these word stems was obtained.

Materials

From this set, 24 familiar words with different spontaneous completion frequencies (ranging from 3 to 37% in the normative study, median=17%) were selected for the actual experiment. Twelve words were designated as 'less common' (frequency of occurrence < 17%) and the remaining twelve as 'common' words (frequency of occurrence > 17%). For the word-completion task, four different sets of six target words (sets 1, 2, 3, and 4) were constructed. These sets, each containing three 'less common' and three 'common' words, were tape-recorded onto four audiotapes (tapes A, B, C, and D) as follows; on each tape, a different combination of two sets was recorded in a cross-over fashion. Tape A contained sets 1 and 2, tape B sets 2 and 1, in that order. Likewise, sets 3 and 4 were recorded onto tape C in that order, and onto tape D in reverse order (see Table 1).

The first set of words on each tape was recorded 5 times, with an interval between each presented set of 10 s filled with silence. The words in this first set were to serve as preoperative stimuli. The second set of words on each tape was recorded 30 times, with an interval between each presented set of 20 s filled with a neutral sound (i.e., bird sounds). The words in this second set were to be presented during surgery. Thus, all tapes contained a 2.45 min presentation of the preoperative words and a 25 min presentation of the intraoperative words, in the female voice of the experimenter. Within each set, the six target words were presented at a speed of one word every 1.5 s, introduced by: 'Please, listen carefully...'. The four tapes were visually identical and had been coded by someone not involved in the experiment to maintain the double-blind character of the study.

The word stems corresponding with all target words were *randomly* dispersed over four new sets. Each new set contained 9 word stems: 3 corresponding with the preoperative target words, 3 with the intraoperative target words, and 3 with distractor (control) words. These new sets of word stems were to serve as test items during the postoperative word-completion tests, and were tape-recorded onto four tapes. The tapes were visually identical and coded P, Q, X, and Y by someone not involved in the experiment. The sets of word stems on tapes P and Q corresponded with tapes A and B; those on tapes X and Y with C and D. The items on tape P were all different from the items on tape Q, and the same applied to tapes X and Y. Each test-tape contained a 1.45 min presentation of nine word stems in the female voice of the experimenter, with an interval between the word stems of 10 s. Table 1 displays an overview of the experimental design.

Table 1 Experimental design

		Tape			
		A	B	C	D
Preoperative	(5 x)	1	2	3	4
Intraoperative	(30 x)	2	1	4	3
Postoperative	day 1	P	Q	X	Y
	day 2	Q	P	Y	X
		recognition task			

Design: pre- and intraoperative tapes A,B,C,D; sets of words 1,2,3,4; postoperative tapes P,Q,X,Y.

Finally, all 24 complete target words were randomly dispersed over one list which was used in the postoperative recognition test. It consisted of 6 preoperative target words, 6 intraoperative target words, and 12 distractor words for each patient. Due to the procedure used, target words for half the patients were distractor words for the other half, and vice versa. The set of 12 distractor words for each patient consisted of 6 distractor words of which the corresponding word stems had also been used in the word stem lists. These distractors were called 'old' distractors. The other 6 distractor words were 'new' words, i.e., words that had not been used in the word-stem sets for that particular patient. The whole list was recorded onto a cassette tape, which contained a 4.35 min presentation of the 24 words in the female voice of the experimenter, with an interval between the words of 10 s.

Not until all data were collected were the codes of the tapes broken.

Subjects

One-hunderd-and-sixteen patients were asked to participate in the experiment, ten of whom refused. A total of 26 patients was excluded from the actual experiment: seven patients could not be exposed to the intraoperative stimuli because the operation schedule was changed; in four cases the surgical procedure took less than 40 min; four subjects had hearing difficulties; four were discharged from hospital one day after surgery; three had received benzodiazepines 30 min before surgery; in three cases a different anaesthetic technique had been used; one patient was too ill at all test sessions, to answer any questions. Thus, 80 informed and consenting patients (ASA 1 or 2) scheduled for elective surgical procedures under general anaesthesia with an expected duration of 40-240 min participated in the experiment. There were 66 women (mean age 39.4 yr, range: 18-66) and 14 men (mean age 35.5 yr, range: 26-55) who met the following criteria: fluent in Dutch, no hearing impairment, no alcohol or psycho-active drug abuse, and no known psychiatric or memory disorder. The study had been approved by the local medical ethics committee. Gynaecological surgery was performed in 31% of the patients (25 women), plastic or reconstructive surgery in 30% (23 women, one man), general or trauma surgery in 20% (12 women, 4 men), neurosurgery (peripheral) in 13% (6 men, 4 women), and orthopaedic surgery in 6% (3 men, 2 women).

Procedure

Each patient completed the state version of the State-Trait Anxiety Inventory[24] in the afternoon before surgery to assess preoperative anxiety. If required, diazepam 5-10 mg (23 patients (29%)), oxazepam 10-20 mg (three patients (4%)), temazepam 10 mg (one patient (1%)), or midazolam 5 mg (one patient (1%)) was given orally the night before surgery. Premedication was with atropine 0.5 mg, i.m., 30 min before the operation.

All patients underwent the following standardized, balanced anaesthesia. Induction: sufentanil (0.5 $\mu g.kg^{-1}$), vecuronium (0.1 $mg.kg^{-1}$), thiopentone (5-7 $mg.kg^{-1}$). Maintenance: nitrous oxide in oxygen 2:1, and isoflurane 0.25-0.5 vol%, continuous end-tidal concentrations isoflurane of 0.2-0.4 MAC (expired); incremental doses of sufentanil and vecuronium were administered every 30 min and when needed. The lungs were mechanically ventilated. At the end of the operation neostigmine combined with atropine was given for reversal of residual muscular relaxation.

Patients were randomly (by means of a random list) assigned to one of the four tapes in a double-blind fashion: tape A (19 patients), tape B (24 patients), tape C (14 patients), and tape D (23 patients), stratified over three age groups (18-35, 36-50, and 51-65 yr) and three levels of expected pain stimulation during surgery (based on the location of surgery and the relative impact and intensity of the operation as assessed by the attending anaesthesiologist). Patients who received tape A or B were tested with the corresponding postoperative tapes P and Q (see *materials*), and those assigned to tape C or D were tested with the corresponding tapes X and Y.

About 15 min before induction of anaesthesia, patients were visited by the experimenter and asked to listen to a tape (A,B,C, or D) with a list of six words, via headphones and a Sony WM-EX 70 walkman. They were instructed not to discuss the contents of the tape with the experimenter or anyone else to maintain the double-blind character of the experiment. This lasted about 5 min. As soon as the preparations for surgery were finished, the headphones were put in position and the patients' ears were covered with a towel. This prevented both patients hearing sounds from the operating room and the experimenter hearing the contents of the tape. Then, from about 15 min after induction, all patients were played the neutral sound (birds) via headphones. Five min after the first incision, the experimental tape (A, B, C, or D) was re-started, and after 25 min bird sounds were again played to all patients for the rest of the operation.

In 68 patients the first postoperative test session took place within 4 h after surgery. The mean interval between the end of surgery and the first postoperative test was 126 min (range: 35-300 min). Twelve patients were too ill to answer any questions on the day of surgery and were tested as soon as possible the morning after surgery ('day 1'). The mean interval between the end of surgery and their first postoperative test was 17 h and 40 min (range: 17 h 10 min-20 h 45 min). Patients were interviewed about explicit recall of both pre- and intraoperative events, with the following questions: "What do you remember about the period before the anaesthesiologist came?", "What is the last thing you remember before you were put to sleep for your operation?", "Did you hear anything during the operation?", and "Did you dream of anything during the operation?" Then the first postoperative tape was played. The order in which the tapes P and Q, or X and Y, were presented on days 1 and 2 was randomized. Subjects were asked to complete (verbally) the nine word stems with the first word that came to mind. Moreover, they were explicitly instructed not to mention a word that came to mind if they remembered having heard the word earlier, either shortly before or during surgery (exclusion instructions). They were asked to name any other word that came to mind should this happen. This session lasted 5 to 10 min. The same instructions were given at the word-completion session on day 2 (including the 12 patients who were too ill on day 1), approximately 24 h after surgery, for the second postoperative tape. Finally, the recognition-task tape was played. The 24 complete words were presented via headphones and patients were instructed to decide, for each word, whether it was a previously presented word or not (i.e., forced choice 'yes/no' recognition task). Subjects were encouraged to take their time and to do their best to remember if they had heard the words before, either right before, or during the anaesthesia. The experimenter was aware of the order in which the words were presented on the recognition tape, but not of the particular contents of the pre- and intraoperative tapes. This session lasted about 15 min.

Any target words named were scored as 'hits', distractor words as 'false positives'. All patients could thus obtain a maximum of 3 preoperative and 3 intraoperative hits, as well as 3 false positives in both completion sessions (day 1 and day 2), and a maximum of 6 preoperative and 6 intraoperative hits, as well as 12 false positives in the recognition task.

To study a possible change in word-completion performance across Day 1 and Day 2 MANOVA-repeated measures was applied to the data of the word-completion task with factors *condition:* preoperative, intraoperative, distractor words; *tape:* tape A, B, C, D; and *day:* day 1, day 2. ANOVA was applied to the data of the forced-choice recognition task (*condition* and *tape*). The 5V module of the BMDP-package was used for both analyses; $p=0.05$ (two-sided) was considered the limit of statistical significance. The data of 'different types of words' were tested by means of Student's t-test.

Results

Free recall

All patients remembered the preoperative presentation of words and the intravenous administration of the anaesthetics for induction. None had any recall of the intraoperative period.

Word completion

For twelve patients, immediate testing was not possible (see *procedure*). They were tested as soon as possible the morning after surgery (mean interval 17 h and 40 min). These patients' scores on the first completion session were treated as scores on day 1.

Table 2 shows the mean proportions of hits on preoperative and intraoperative items and of false positives (baseline performance) for word completion. Proportions are the mean number of hits or false positives divided by the maximum number of hits or false positives that could be obtained (during a particular test session).

Overall, there were no significant interactions between condition, tape, and day. No significant main effects of tape and day were found, indicating that there was no difference in performance across tapes or days. A significant main effect of condition was found, $p=0.03$, indicating significant differences in performance on the three conditions. We then compared number of hits or false positives in the three conditions (preoperative, intraoperative, distractor) pairwise. Comparison between intraoperative hits and number of false positives (baseline-performance) revealed that patients were more likely to complete word stems with words presented during anaesthesia than to distractor words ($p=0.006$). In sum, this finding indicates unconscious memory.

Comparison of preoperative hits with the number of false positives revealed that relative to the baseline condition, patients failed to exclude all preoperative words (n.s). Had they been successful in excluding words, then the preoperative hit-ratio would have been below baseline.

Comparison of the preoperative hits with the intraoperative hits showed that contrary to our hypothesis, patients did not exclude more preoperatively than intraoperatively presented words (n.s).

Table 2 Mean proportions (± SD) of hits/false positives on word completion and recognition.

		Condition		
		Preoperative	*Intraoperative*	*Distractor*
Word completion	Day 1	0.19(±0.22)	0.23(±0.25)	0.14(±0.21)
	Day 2	0.16(±0.19)	0.21(±0.23)	0.15(±0.21)
Recognition	Day 2	0.75(±0.24)	0.20(±0.20)	0.11(±0.16)

Recognition

The mean proportions of hits on preoperative and intraoperative items and of false positives were 0.75, 0.20, and 0.11, respectively. ANOVA with factors *condition* (preoperative, intraoperative, distractor) and *tape* (tape A,B,C,D) did not reveal an interaction between condition and tape, indicating that memory performance did not differ across tapes. As expected, a significant main effect of condition, $p<0.001$, was found.

Performance differed significantly across the three conditions. Number of hits and false positives were compared between conditions. Patients recognized considerably more intraoperatively presented target than distractor words ($p<0.001$). Sixty percent of the intraoperatively presented words that were designated 'recognized' were words that had not been mentioned by the patients during the word completion sessions. Patients reported in general that they were not very confident about their guesses during the recognition task.

As expected, comparison of recognition performance on the preoperative words with performance on intraoperative words revealed that patients recognized considerably more preoperative (though not all) than intraoperative words ($p<0.001$).

Common and less common words

The mean number of common words generated on the word-completion task was compared with the mean number of less common words generated for each condition separately (preoperative, intraoperative, distractor). Note that word stems were randomly balanced across the two days. With regard to the intraoperative target items, word stems corresponding with common words were significantly more often completed with target words than word stems belonging to less common words, $p<0.05$. There was no effect of type of word on the preoperative target items, and on the distractor items.

The same comparison was made for the recognition task between the mean number of recognized common words and the mean number of recognized less common words, for the three conditions. Analysis of the data of this task revealed no effects of type of word.

Finally, for each word stem the number of false-positives on the word-completion task (i.e., baseline performance) was compared with completion frequencies of the same items determined in the normative study. This comparison yielded no significant differences in completion frequencies between both data sets.

Other variables

Mean preoperative anxiety was 43.6 and hence slightly elevated. There was no relation between hit scores on the word-completion and the recognition task on the one hand, and preoperative anxiety or estimated pain intensity on the other. The same applied to age and gender.

Discussion

In contrast to an earlier study by our group[13] in which we could not demonstrate memory for material presented during balanced anaesthesia, memory effects were found in the present study. In the previous study, patients showed no memory for less-common category exemplars measured by means of a category-generation task. In the present study word completion- and forced-choice recognition tasks, in combination with familiar words as stimulus material, were successful instruments in the assessment of memory in anaesthesia.

Exclusion instructions were used in the word-completion task to find out if memory for material presented during anaesthesia can be regarded as unconscious, rather than a result of temporarily 'light' anaesthesia. The logic underlying exclusion instructions implies that unconscious memory is demonstrated whenever subjects fail to follow the instruction to exclude previously presented material during a subsequent memory task. In other words, whenever performance is better than baseline, there is evidence for unconscious memory. In contrast, when performance is below baseline, there is evidence for conscious memory[22]. With regard to the present study, we assumed that patients would have conscious control over the preoperative words and consequently exclude those words. Our results show a different pattern. Performance on the preoperative items did not differ from baseline performance, indicating that memory for the preoperative words was not 'perfect'. In retrospect, this is perhaps not surprising if one takes into account the anxiety and stress patients experience shortly before surgery. It seems likely that this affects patients' concentration. Moreover, patients were not explicitly instructed to remember these words in order to match the pre- and intraoperative situations with respect to the passive condition of the patients. Although the words had been repeated five times to promote learning some were nevertheless forgotten. Likewise, we expected that patients would have unconscious memory for the words presented during anaesthesia and consequently fail to exclude these words on the word completion task. Performance on the intraoperative items was in accordance with these expectations; the number of failures to exclude was significantly greater than baseline level which indicates unconscious memory (see also Merikle and Joordens[22]). In summary, our findings suggest that unconscious memory was more dominant than conscious memory for the intraoperative material.

The most striking outcome of the present study is the demonstration of memory for intraoperative material by means of a forced-choice recognition task. Our findings are in contrast to previous results[12,25,26] and support the idea that forced-choice recognition is sensitive to material presented during general anaesthesia[18-20]. The nature of the instructions ('unforced' vs. 'forced') at test determines the 'success' of this task; if patients are instructed to respond to each item, guessing behavior is increased and apparently patients tend to be quite accurate in their guesses. On the other hand, if patients are allowed not to respond if unsure, or in other words not specifically encouraged to guess, (unconscious) information that may contribute to correct responses may be suppressed. In our study, the inclusion of preoperative words, i.e., words that patients could easily recognize, may have increased patients' confidence so that they were more prone to say 'yes' to intraoperative words on the basis of very vague feelings of familiarity. Mandler[27] suggested that the recognition of a previously presented item is partly based on feelings of familiarity. In fact, according to Mandler, two simultaneous processes are invoked when a subject has to recognize an item. The first process indeed retrieves the 'familiarity' value of the item and the second mechanism engages in a search and retrieval process that attempts to determine whether the target item was originally presented. These processes are assumed to operate independently of each other. Mandler's recognition memory model helps explain our recognition task results because it distinguishes between remembering that is initiated and guided by a conscious intention versus remembering guided by feelings of familiarity. As stated earlier, it seems likely that patients in our study made the decisions about previous presentation of the intraoperative words on the basis of feelings of familiarity, but we have no empirical data to support this.

We presented patients with both common and less common (though familiar) words in order to study the effect of type of words on memory performance. On the basis of the present and earlier findings[12,13] we conclude that type of words (common vs. less common words) has an effect on word-completion performance, but not on recognition performance. Moreover, we suggest that familiarity with the information surgical patients are exposed to may underlie memory for intraoperative events.

Our findings yield evidence for unconscious memory immediately after surgery and 24 h later, indicating that these memory effects last at least 24 h. On the basis of several negative findings, we have argued that implicit memory during anaesthesia is an elusive, transient phenomenon[13]. However, the results of a study by Schwender and colleagues[23], who found memory effects after three to five days postoperatively, and the present evidence for unconscious memory after 24 h demonstrate that these effects can be long lasting. The representations in memory of the words we presented apparently remained activated for at least 24 h. In our view, this finding may form a starting-point for further research into the duration of implicit-memory effects.

Although we found evidence for unconscious memory during general anaesthesia by means of two different memory tasks, we believe that the phenomenon still requires study. Given that the results in this field of research are far from uniform, we agree with Ghoneim and Block[1] and Caseley-Rondi and colleagues[18] that investigators in this area should attempt to replicate positive results.

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CHAPTER 5

Memory during anaesthesia and the effect of number of stimulus presentations

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Abstract

Memory for words presented during general anaesthesia was studied in surgical patients undergoing elective procedures under balanced anaesthesia. Before and during surgery patients were presented, via headphones, with common words. To study the effect of number of presentations on unconscious memory, one list of words was presented once, and a second list of words was presented thirty times during anaesthesia. At the earliest convenient time after surgery (within 4 h) memory for the words was tested by asking patients to complete verbally presented word stems with the first word that came to mind. Part of the word stems corresponded with the experimental words (target items). The remaining wordstems served as control items (distractors). Twenty-four hours after surgery patients were requested to perform a "yes/no" forced-choice recognition task to assess recognition memory for both the pre- and intraoperative words. Memory for the words presented during anaesthesia was demonstrated immediately after surgery and 24 h later by means of both tasks. The word-completion results revealed that memory was most apparent after one presentation. Varying number of presentations had no effect on recognition memory.

Introduction

Patients during anaesthesia seem able to encode and store information in memory without postoperative recollections[1-5]. The preconditions for the occurrence of such memory effects are type of anaesthetic technique[6], nature of the intraoperative stimuli and type of memory task[7-9], interval between stimulus presentation and postoperative test[10], and similarity of sensory modality between learning phase and test phase[9]. Another important aspect of the assessment of memory in anaesthesia is the measurement of depth of anaesthesia[11]. A reliable indicator of anaesthetic adequacy not yet being available, evidence for material presented during anaesthesia can always be attributed, theoretically, to a temporarily light anaesthesia and judgements about the nature (conscious or unconscious) of memory in anaesthesia are almost impossible to make[1,11]. In order to find convincing evidence of unconscious memory for material presented during anaesthesia attention should be paid to the best possible assessment of anaesthetic adequacy.

In Study 2 (Chapter 4) a method derived from cognitive psychology[12,13], i.e., the *exclusion task*, was employed to distinguish between conscious and unconscious contributions to postoperative word-completion performance. The distinguishing characteristic of this task is that subjects are instructed *not* to use certain responses when performing a particular memory task. The exclusion-task results of Study 2 revealed that patients were unable to exclude the intraoperative words, which was considered evidence of unconscious memory, and showed partial exclusion of preoperative words, indicating that some of the preoperative words were forgotten. The latter finding was explained by suggesting that patients were either too anxious shortly before surgery to concentrate on the preoperative words, or had forgotten words because they had not explicitly been instructed to remember them (see Chapter 4). In the present study we instructed patients during the preoperative phase of the present study to form a sentence, mentally, with each word. This mental operation requires more cognitive effort than merely listening to a word[14] and consequently might result in enhanced memory performance.

In Study 2, we found evidence of memory for words presented during balanced anaesthesia by means of forced-choice recognition and word completion with exclusion instructions. Both tasks are considered direct tasks because subjects are instructed to think back to the study phase to recall or recognize previously presented material. Indirect memory on the contrary is measured by a facilitation in task performance attributable to previous learning. Until recently, only indirect and not direct tasks were believed to be capable of measuring memory in general anaesthesia, because indirect tasks do not require memory of the intraoperative period[8,9,15]. Recent studies[1,16,17] have demonstrated that forced-choice recognition is an exception to this rule. The 'forced' character of the task is critical in this context; because subjects are requested to respond to *each* item guessing behaviour is increased, and subjects tend to guess accurately[1,16,17]. Correct recognition of previously presented items is not based on conscious recollection but on (vague) feelings of familiarity[10,18]. As the demonstration of memory for intraoperative material by means of a forced-choice recognition task is relatively new, we felt that a replication of this finding would be appropriate.

A final issue is the number of stimulus presentations necessary to result in memory effects. Most anaesthesia studies have used multiple presentations and it is still unclear if a single presentation of a stimulus is sufficient to cause a memory effect. Experiments in which the number of presentations was manipulated did not yield a clear picture. Winograd, Sebel, Goldman, and Clifton[18] and Bonebakker, Bonke, Klein, Wolters, and Hop[21] varied the number of stimulus presentations but failed to find any memory effects. Block, Ghoneim, Sum Ping, and Ali[20] found that nonsense words that had been presented frequently (at most 16 times) were preferred more on a postoperative preference task than words presented less frequently, but this was not replicated in additional control tests. In the present study the number of stimulus presentations was varied by presenting words either one or thirty times during anaesthesia. To study the possibility that words presented once are 'overshadowed' during intraoperative presentation by words presented 30 times, we added an experimental condition in which all words were only presented once (see also Brown, Best, Mitchell, and Hoggard[22]).

To summarize, the main objective of the present study was to demonstrate memory for words presented during balanced anaesthesia. More specific, our aim was to replicate the findings in Study 2, using the same experimental procedure. We employed the exclusion task in order to get an indication of conscious and unconscious contributions to postoperative memory performance. The underlying assumption was that if patients were unable to exclude target words, there would be evidence for unconscious memory. The second aim of our study was to assess the effect of number of stimulus presentations on memory in anaesthesia.

Methods

Materials

In a previous study[1] (Chapter 4) spontaneous completion frequencies had been collected for 42 different word stems among representative surgical patients (in the same hospital as in the actual experiment). On the basis of these norms 24 familiar words had been selected for use in Study 2, which were again used in the present study. Twelve of these words were 'common' words (frequency of occurrence in normative study > 17%), the remaining 12 were 'less common' (frequency of occurrence < 17%). Four different lists (1-4) of six target words were constructed, each consisting of three common and three less common words. The lists were tape-recorded onto four audiotapes (A-D) counterbalanced in different combinations (table 1). The words from the list that was not recorded on a particular tape (e.g., list 4 for tape A) were to serve as distractor words on the postoperative tests. Performance on these items would reflect baseline performance.

The first six words on each tape, which were to serve as the preoperative stimuli, were recorded with a 15-s interval between each word filled with silence. On tapes A, C, and D, the second list of words was recorded once and the third list thirty times. These words were to be presented during surgery. Between each presented list there was an interval of 20 s filled with a neutral filler sound (i.e., bird sounds). Each tape contained a 2-min presentation of the preoperative words and a 25-min presentation of the intraoperative words. On tape B, the second and the third lists were *both* recorded *once* with a 10-min interval between the first (preoperative stimuli) and second list, and 20 s between the second and the third list (see table 1). These intervals were again filled with bird sounds. The 'Tape B' condition was included to study the possibility that words that had been presented once in the other conditions would be 'overshadowed' by words that had been presented 30 times during the operation. In the 'Tape B' condition, stimulus presentation lasted 1 min. The rest of this and the other tapes was filled with bird sounds.

Within each list, the six words were recorded at a speed of one word every 1.5 s and preceded by: 'Please, listen carefully...'. To maintain the double-blind character of the study, the four tapes were visually identical and had been coded by someone not involved in the study.

For the postoperative word-completion task, a tape containing 12 word-stems was prepared. For each patient three word-stems corresponded with the preoperative target words, 6 with the intraoperative target words (3 from each intraoperative list), and 3 with distractor words. Duration of this tape was 2 min.

Table 1 Experimental design

		Tape			
		A	B	C	D
Preoperative	(1 x)	1	2	3	4
Intraoperative	(1 x)	3	4	2	1
Intraoperative	(30 x)	2	1*	4	3
Postoperative	day 1	word completion			
	day 2	forced-choice recognition			

Design: pre- and intraoperative tapes A,B,C,D; lists of words 1,2,3,4. *List 1 on tape B was presented once instead of 30 x.

Finally, all 24 complete target words were randomly dispersed over one list, which consisted of 6 preoperative target words, 12 intraoperative target words, and 6 distractor words for each patient. The list was tape-recorded and lasted 4.35 min. All recordings were in the female voice of the experimenter.

Not until the experiment was finished were the codes of the tapes broken.

Subjects

After approval by the local medical ethics committee, one-hundred-and-one surgical patients (ASA 1 or 2) were approached for participation in the experiment. Seven refused, 14 patients were excluded from the study: in five cases the operation schedule was changed, in four cases a different anaesthetic technique had been used, two patients had hearing impairments, one had a history of alcohol abuse, one had received benzodiazepines 30 min before surgery, and one was too ill to be tested. Thus, 80 informed and consenting patients scheduled for elective surgical procedures under standardized, general anaesthesia with an expected duration of 40-240 min, participated in the study. None had hearing difficulties, a history of alcohol or psycho-active drug abuse, or a known psychiatric or memory disorder. They were 52 women (mean age 39.8 yr, range 18-64) and 28 men (mean age 40.6 yr, range 23-63). All were fluent in Dutch.

Neurosurgery (peripheral) was performed in 30 % of the patients (9 women, 15 men), general or trauma-surgery in 26% (14 women, 7 men), plastic or reconstructive in 20% (14 women, 2 men), orthopaedic in 17% (10 women, 4 men), urological in 4% (3 women), and gynaecological in 3% (2 women).

Anaesthesia

If required, tranquillizers were given orally the night before surgery: diazepam 5-10 mg (23 patients, 29%), oxazepam 10-20 mg (6 patients, 7%), lorazepam 1 mg (1 patient, 1%), or levomepromazine 0.5 mg (1 patient, 1%). Premedication was with atropine, 0.5 mg i.m., approximately 30 min before surgery.

Anaesthesia was induced with thiopentone (4-7 $mg.kg^{-1}$), vecuronium (0.1 $mg.kg^{-1}$), and sufentanil (1-1.5 $\mu g.kg^{-1}$, 76 patients), or alfentanil (20-30 $g.kg^{-1}$, 4 patients), depending on the type of surgery. One patient was induced with 20 mg etomidate instead of thiopentone, because of a history of cardiac arrhythmias. When consciousness was lost, the trachea was intubated. Anaesthesia was maintained with nitrous oxide in oxygen (2:1), isoflurane 0.25-0.50 vol%, and incremental doses of vecuronium and sufentanil or alfentanil (4 patients) when needed. End-tidal concentrations of isoflurane were continuously maintained at 0.2-0.4 MAC. The lungs were mechanically ventilated. At the end of the operation, neostigmine combined with atropine was given for reversal of residual muscular relaxation and the isoflurane and nitrous oxide administration was discontinued. As soon as patients responded adequately to instructions and breathed spontaneously, the trachea was extubated.

Procedure

All patients were asked to complete the state version of the State-Trait Anxiety Inventory[23] on the afternoon before surgery. Patients were randomly (by means of a random list) assigned to one of the four tapes in a double-blind fashion: tape A (25 patients), B (23), C (13), and D (19), stratified over three age groups (18-35, 36-50, and 51-65), and three levels of expected pain stimulation during surgery (based on the location of surgery and the relative impact and intensity of the operation as assessed by the attending anaesthesiologist).

Approximately 15 min before induction of anaesthesia, patients were visited by the experimenter and asked to listen to a 2-min tape containing six words, via headphones and a Sony WM-EX 70 walkman. They were instructed to mentally form a sentence with each word, but, to maintain the double-blind character of the experiment, not to mention any sentences or words to the experimenter or anyone else. This session lasted about 5 min. Three patients were not presented with the preoperative words because the operation schedule had changed.

As soon as the preparations for surgery were finished, headphones were put into position and the patients' ears were covered with a towel. This prevented the experimenter and the operating room personnel from hearing the contents of the tape. From about 15 min after induction, all patients were played the neutral (bird) sounds via headphones which prevented patients from hearing sounds from the operating room before and after stimulus exposure. Five min after the first incision the experimental tape (A, B, C, or D) was re-started, and after 25 min the tape with bird sounds was again played to all patients for the rest of the operation.

In 72 patients the first postoperative test (day 1) took place within 5 h after surgery (mean interval between end of surgery and test: 137 min; range 40-325 min). Eight patients were too ill at the day of surgery to answer any questions and were tested the next morning, within 20 h after surgery. Prior to the word-completion task, patients were interviewed about explicit recall of the preoperative and intraoperative periods with the following questions: "What do you remember about the period before the anaesthesiologist came?", "What is the last thing you remember before you were put to sleep?", "Do you remember anything about the operation?", "Did you hear anything during the operation?", and "Did you dream anything during the operation?" Then the tape with 12 word stems was played via headphones. Patients were instructed to complete each word stem with the first word that came to mind. Moreover, they were explicitly instructed not to name the words they remembered having heard earlier, either before or during anaesthesia (exclusion instructions). They were asked to name any other word that came to mind in such cases. In order to investigate whether patients' had understood and followed the exclusion instructions, they were asked after the test if they had deliberately excluded particular words.

The forced-choice 'yes/no' recognition task took place approximately 24 h after surgery in 73 patients; two patients were too ill to take the test, two were discharged from hospital, and three had not heard the words presented preoperatively. Patients were presented, via headphones, with 24 complete words and instructed to decide for each word whether or not it was a previously presented word. They were encouraged to take their time and do their best to remember if they had heard the words either right before, or perhaps during anaesthesia. We encouraged them to guess in cases in which they were not sure. When the test was finished, patients were asked how confident they were about their responses. The experimenter was aware of the order in which the words were presented, but not of the actual contents of tapes A, B, C, and D. This session lasted about 15 min.

Statistical analyses

For the postoperative tasks, words named or recognized were scored as 'hits' if they were target words, and as 'false positives' if they were distractors. A maximum of 3 preoperative and 6 (2x3) intraoperative hits, and 3 false positives could be obtained on the word-completion task. A maximum of 6 preoperative and 12 intraoperative (2x6) hits, and 6 false positives on the recognition task.

To answer the first research question (i.e., *"Is there any memory for intraoperatively presented words?"*) the data of all patients (N=80) were analyzed by means of ANOVA using the 5V module of the BMDP-package, with factors *condition* (preoperative, intraoperative, distractor) and *tape* (A, B, C, D), while the data of the 1x presentation and 30x presentation were collapsed. Subsequently, the data of the 57 patients who had been exposed to both 1 and 30 presentations were analyzed to answer the second research question (i.e., *"Does memory for words presented once differ from memory for words presented 30 times?"*) with factors *condition* (intraoperative 1x, intraoperative 30x, distractor) and *tape* (A, C, D). Finally, the data of the 23 patients that had been exposed to tape B (two 1x presentations) were analyzed with Student's t-test for paired samples.

To find out if common words have an advantage over less common words, data on the occurrence of words were analyzed by means of Student's t-test for independent samples. P=0.05 (two-sided) was considered the limit of statistical significance.

Results

All patients remembered the preoperative presentation of words and the intravenous administration of the anaesthetics for induction. None had any recall of the intraoperative period. Both the word-completion and the forced-choice 'yes/no' recognition task showed evidence of unconscious memory during anaesthesia.

Word completion

Because word completion performance does not change significantly during the first 24 h postoperatively (Chapter 4), the scores of the 8 patients that were tested the morning after surgery were included in the analysis of the word-completion data.

Table 2 (upper row) shows the mean proportions of hits and of false positives of all patients (N=80, tapes A, B, C, D) for word completion. Proportions are the mean number of hits/false positives divided by the maximum number of hits/false positives that could be obtained (during a particular test session).

Tapes A,B,C,D: There were no significant interactions between *condition* and *tape*, indicating that there was no difference in performance across the tapes. A significant main effect was found for *condition*, p=0.025, indicating significant differences in performance across the three different conditions. Pairwise comparison of the hit- and false positive-ratios in the three conditions (a) intraoperative with distractor; b) preoperative with distractor; c) preoperative with intraoperative) revealed the following results. a) A significant main effect of the factor *condition*, p=0.04, indicating that patients' performance for the intraoperative-condition was significantly above baseline. This suggests memory for the words that were presented *during* anaesthesia. b) Although the absolute number of preoperative hits was slightly below baseline (mean 0.39 versus 0.43

words), there was no main effect of *condition* indicating that contrary to our expectations patients did not exclude all preoperative words. Fewer preoperative hits than false positives would have indicated a large amount of conscious control over the words that were presented before surgery. However, patients reported in general that they had deliberately excluded one or more preoperative words. c) Mean number of excluded intraoperative words differed significantly from the mean number of excluded preoperative words, p=0.013, indicating that patients suppressed more preoperative than intraoperative stimulus material. In other words, there was more conscious control over the words presented before relative to the words presented during anaesthesia.

Tapes A,C,D (N=57): Mean numbers of hits on intraoperative items presented once and thirty times were 0.71 and 0.47, respectively; mean number of false positives was 0.38. There was no significant interaction or main effect of *tape*, i.e., performance on the three item-types did not differ across tapes A, C, and D. There was, however, a significant main effect of *condition*, p=0.005, indicating that performance differed significantly for the intraoperative(1x), intraoperative(30x), and distractor words. Pairwise comparisons revealed that performance on once presented words was higher than baseline performance (0.71 and 0.38 words, respectively, p=0.004), whereas performance for 30x presented words was not (0.47 vs. 0.38, n.s.).

Tape B (N=23): Mean numbers of hits and false positives were 0.68, 0.64, and 0.50 for the intraoperative (lists 1 and 4, see experimental design) and the distractor items, respectively. Neither for list 1, nor for list 4 did the mean number of hits differ significantly from baseline performance. Though not significant, this pattern of results resembles the overall pattern: mean number of hits in both intraoperative conditions was higher than that of false positives.

Recognition

The data of 73 patients (see procedure) were included in the ANOVA for the forced-choice "yes/no" recognition task. The second row of table 2 shows the mean proportions of hits and false positives (tapes A, B, C, and D) for recognition.

Tapes A,B,C,D: There was a marginally significant *condition* x *tape* interaction, p=0.04, mainly caused by an inconsistent pattern of results across the four tapes on the distractors: mean numbers of false positives were 0.70, 1.56, 1.42, and 0.67 for tapes A, B, C, and D, respectively. The main effect of *tape* was not significant (p=0.06).

As expected, there was a significant main effect of *condition*, p<0.001, mainly caused by the high number of recognized preoperative words (4.75 words) relative to recognition in the other conditions (1.41, and 1.08 words, for intraoperative words and distractors, respectively). The number of hits and false positives were compared between conditions. Comparison between intraoperative hits and false positives revealed a significant *condition* x *tape* interaction (p=0.01), again caused by the different false-positive ratios across the four tapes. The main effect of *condition* was significant, p=0.012, indicating that more intraoperatively presented words were recognized than distractors recognized falsely. Sixty-three percent of the intraoperatively presented words that were 'recognized' were words that had *not* been mentioned by the patients during the word-completion task. Patients reported in general that they were quite confident about their guesses.

As expected, comparison between preoperative hits and false positives showed a significant main effect of *condition*, p<0.001; patients recognized considerably more (though not all) preoperative than the number of falsely recognized distractors. The same result was found for preoperative vs. intraoperative hits; patients recognized more preoperative than intraoperative words (p<0.001). There was no interaction with *tape* in the latter comparisons.

Tapes A,C,D (N=51): The mean numbers of hits for words presented 1x and 30x, were 1.31 and 1.39, respectively, mean number of false positives was 0.86. ANOVA for the data of this group yielded a significant *condition* x *tape* interaction, p=0.023, indicating a difference in performance across the three conditions caused by different recognition scores on the tapes. Inspection of the data showed that this interaction effect was caused by divergent performance across tapes A, C, and D in the intraoperative(30x)-condition: mean numbers of hits were 1.84, 1.15, and 1.10 words for tapes A, C, and D, respectively. The main effect of *condition* was significant, p=0.006, indicating that performance across the three different conditions differed significantly. The main effect of *tape* was not significant.

Comparison of the intraoperative(1x)-condition with baseline performance yielded a main effect of *condition*, p=0.005; patients recognized more once presented words than distractors. This effect did not interact with *tape*. Comparison of intraoperative(30x) with baseline performance yielded a significant *condition* x *tape* interaction effect, p=0.003

(see previous paragraph), and a significant main effect of *condition*, p=0.004. Therefore, number of word presentations does not have a clear effect on recognition memory. There was no main effect of *condition* in the 1x vs. 30x comparison; recognition after one presentation did not differ significantly from that after 30 presentations. There were no main effects of *tape*.

Tape B (N=22): Mean numbers of hits and false positives were 2.05, 1.05, and 1.68 for intraoperative lists 1 and 4 and distractors, respectively. There were no significant differences, i.e., there was no evidence of recognition memory in this subgroup. Contrary to the word-completion performance in this group, there was no tendency to score more intraoperative hits than false positives.

Table 2 Mean proportions (± SD) of hits/false positives on word completion and recognition (tapes A, B, C, D).

		Condition		
		Preoperative	*Intraoperative*	*Distractor*
Test	Word completion	0.13(±0.20)	0.20(±0.19)	0.14(±0.20)
	Recognition	0.79(±0.20)	0.24(±0.17)	0.18(±0.20)

Common and less common words

Mean number of generated common words was compared with that of generated less common words on the memory tasks. A distinction was made between the three item types (i.e., preoperative, intraoperative and distractor items) and word completion and forced-choice recognition were analyzed separately. Student's t-tests did not yield any significant differences between numbers of generated common and less common words for either of the three item types for either memory task. In other words, there was no significant advantage of common words over less common words and vice versa. This was true despite that common words were generated 61 times on the intraoperative items of the word-completion task, whereas less common words 33 times. The opposite tendency was found for the intraoperative items of the recognition task; subjects designated 70 less common words as recognized and 55 common words.

Finally, the completion frequencies for each word stem that served as a distractor in the word-completion task were compared with completion frequencies of the same items in the normative set (see materials). This comparison yielded no clear differences in completion frequencies between both data sets.

Other variables

Mean preoperative anxiety was 44.6, which is quite elevated. ANOVA with factors *condition* (preoperative, intraoperative, distractor) and *anxiety* (moderate, elevated) revealed no relation between hit scores on word completion and recognition on the one hand, and preoperative anxiety on the other. The same applied to gender.

ANOVA of the word-completion data and estimated pain intensity with factors *condition* (preoperative, intraoperative, distractor) and *pain* (low, medium, high) revealed a significant *condition* x *pain* interaction with regard to preoperative items ($p=0.03$): mean numbers of preoperative hits were 0.43, 0.24, and 0.63 for 'low', 'medium', and 'highly' painful procedures, respectively. Patients who had undergone the most painful procedures had more difficulty in excluding preoperative words within 5 h postoperatively than other patients.

ANOVA of the recognition data with factors *condition* (preoperative, intraoperative, distractor) and *age* (18-35, 36-50, 51-65 yrs) revealed a significant *condition* x *age* interaction for recognition of preoperative words ($p<0.001$). Mean numbers of hits on the preoperative items were 5.31, 4.75, and 3.95, for young, middle-aged, and older patients, respectively. This indicates that recognition of words presented shortly before surgery gradually decreased with age. No other significant relations between memory performance and anxiety, gender, age, or pain were found. Apparently conscious, but not unconscious memory processes are affected by variables such as pain and age.

Discussion

The most important outcome of this study is the successful replication of the major findings in our previous study[1] (Chapter 4). Again, we demonstrated memory for words presented during balanced anaesthesia by means of a word-completion task and a 'yes/no' forced-choice recognition task. In addition, we found an effect of number of intraoperative stimulus presentations on word-completion performance; unconscious memory was apparent after one presentation of target words during anaesthesia but could not be demonstrated after 30 presentations. Number of intraoperative presentations had no effect on recognition performance 24 h postoperatively.

The present results show that this particular arrangement resulted in further evidence for memory during anaesthesia. On the basis of both studies we suggest that presentation of familiar words before and during balanced anaesthesia, and the postoperative assessment of both conscious and unconscious memory by means of word completion with exclusion instructions and forced-choice recognition, are a successful procedure to demonstrate memory during anaesthesia. The fact that the word-completion data are nearly identical in both studies (i.e., mean baseline performance 0.43, mean number of intraoperative hits (n=80) 0.68 and 0.61) indicates that we are dealing with a replicable effect on word completion. Recognition performance was somewhat different; baseline performance and mean number of intraoperative hits were both higher in the present study (1.08 vs. 0.66 false positives, and 1.41 vs. 1.20 hits).

In both studies, patients were instructed to respond to each item on the recognition task. This 'forced' character of the task stimulates subjects to guess, even if unsure, and may result in accurate guesses[1,10,17]. Indeed, patients were explicitly encouraged to guess if unsure and this may have led to a more liberal response strategy.

We have argued that an essential aspect of the experimental procedure we employed is the inclusion of a preoperative presentation of words[1]. We initially included the presentation of preoperative stimuli to validate the exclusion task. In order to demonstrate a dissociation between conscious and unconscious memory processes (which is the general idea underlying the exclusion task) memory tasks need to trigger both conscious and unconscious information in memory. In retrospect, an important side-effect of the presence of familiar stimuli (i.e., items that subjects recognize) during the test phase is that the subjects' confidence is enhanced. The results of the forced-choice recognition task help clarify this point. During this task, patients were presented with a word list that included a number of words they would definitely recognize, i.e., the words that had been presented shortly before surgery. After this task the majority of patients stated that they were quite confident about their answers (which included the intraoperative items they had recognized). Although we have no empirical data to support this, their confidence seems to be based on the presence of words they recognized from the preoperative period. Our observations in patients who had not been exposed to the preoperative words showed that they did not recognize a single item in the list. In other words, forced-choice yes/no recognition may be insensitive to material presented during anaesthesia if none of the test items refer to a preceding conscious learning episode. Therefore, it is important to consider that recognition of unconscious material may depend on the presence of recognizable items.

Another important objective of this study was whether number of stimulus presentations affected memory in anaesthesia. In order to assess such an effect we presented patients with two different lists of words during anaesthesia. The first list was presented once, five minutes after the first incision, followed by 30 presentations of the second list, with a 20 s interval between both stimulus sets. Our results show that for word completion, memory effects occurred for the once presented words whereas we were unable to show such effects for the 30x presented words. The latter result is in contrast with earlier findings[1-4,20] and might suggest that in the present study intraoperative processing of information took place during the first minutes of surgery when the first list was presented. It is conceivable that patients were more 'aroused' by pain stimuli during the first part of surgery and consequently processed more information than they did in the rest of the intraoperative period. However, two other findings argue against this assumption. First, the word-completion data of the subgroup that was exposed to one presentation of two lists indicate a tendency to name more intraoperative words than distractors. Contrary to the three other experimental conditions, in this condition words were presented 15 min after the first surgical incision. Second, there was no clear effect of number of presentations on recognition performance. Mean numbers of hits were identical for 1x and 30x presented words in the recognition task (1.39 in both cases). It must be noted however that the effect for the 30x presented words was not consistent across the four tapes.

A different explanation is that the words in the first list might have been perceived better than the later ones, and have consequently become better candidates for coming up as completions to word stems during the word completion task than others. This 'primacy effect'[24] refers to the phenomenon that when a list of homogenous items is learned items at the beginning of a list have a relative superiority over those in the middle because they received more attention during the learning phase. Such an advantage of the first words over later words within each list of the word-completion task would have supported this assumption, but no such pattern could be detected in the word-completion data. In addition, serial position effects (first and last items are remembered best) are characteristic for explicit memory processes but not for implicit memory[25].

A final possibility is that patients suppressed the words that were presented 30x either because they were instructed to do so (exclusion instructions) or because they unconsciously associated the material with an aversive period in the surgical procedure[22,26]. The first assumption suggests that there must have been some control over the words that were presented 30x. Performance for the 30x presented words was close to baseline (i.e., 0.47 hits versus 0.43 false positives). According to the logic underlying the exclusion task, performance below baseline level is an indication of conscious memory[12], suggesting that in the present case only some of the words may have been excluded because patients felt they had heard the words before. The decision to exclude words that 'ring a bell' could be based on the same process as that underlying the recognition of intraoperative words[1,10]; the 'familiarity value' of an item is retrieved and at the same time a retrieval process determines whether the target item was originally presented. According to Mandler[18] the first mechanism is more inferential and automatic in nature. It is possible that not only recognition judgements but also the judgement to exclude words is based more on vague feelings of familiarity than on conscious memory of a previous learning episode. At this moment there is no empirical data to either support or invalidate the assumption that some inhibitory process affects the retrieval of information perceived during surgery.

Most recent experiments[1-5,20] have demonstrated memory effects after multiple presentations, suggesting that the null finding is spurious. Future studies might concentrate on memory effects with different numbers of presentations throughout the course of surgery. On the basis of the present study, we conclude that one presentation of words is sufficient to cause a memory effect and that number of presentations has an effect on word completion but not on recognition performance 24 h postoperatively.

Exclusion instructions in the word-completion task resulted in performance below baseline on the preoperative items (0.39 versus 0.43), but this difference was not significant. Despite the fact the patients were instructed to mentally form a sentence with the preoperative words in order to 'force' them to pay more attention to the words and hence improve exclusion performance, they hardly performed below baseline. Given the stress and anxiety patients experience shortly before surgery this finding is perhaps not surprising[1]. However, compared to performance in our previous study (0.57, versus 0.39 in the present study) exclusion of preoperative words was considerably better, which indicates a moderate effect of the instruction to form sentences.

Likewise, we expected that patients would have no conscious control over the words presented during anaesthesia and consequently fail to exclude these words on the word completion task. Our hypothesis was supported by performance on the words that had been presented once during surgery; the number of failures to exclude these words was significantly greater than baseline level. This indicates that where memory for these words is concerned, unconscious influences are greater than conscious influences. Performance on the 30x presented intraoperative items was however not significantly greater than baseline. On the basis of this study, the possibility that patients deliberately excluded some of the intraoperative words cannot be ruled out. In other words, exclusion instructions alone did not provide us with a satisfactory estimate of the amount of conscious control over the 30x presented words. We therefore conclude that a future experimental design needs to be extended with a condition in which all conscious influences are removed from memory performance[13] (see Chapter 6).

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CHAPTER 6

General discussion

The general of aim of the present project was to find out if surgical patients can hear and process information during general anaesthesia. Moreover, the effects of specific stimulus-characteristics on memory were tested to determine the circumstances under which these memory effects occur. The results of this project have implications for psychological research into perception without awareness.

Stimuli and tasks

Memory for words presented during 'balanced' anaesthesia was demonstrated in Studies 2 and 3, but not in Study 1. The general conclusion that can be drawn on the basis of the findings from all three studies is that Category generation in combination with less prototypical exemplars as intraoperative stimuli (Study 1, Chapter 3) is less sensitive to memory for intraoperative material. On the contrary, word completion and forced-choice 'yes/no' recognition with both common and less common words as stimuli, were sensitive and reliable instruments to assess memory in anaesthesia. In sum, we conclude that unconscious memory is possible during general anaesthesia and can be revealed by means of a word-completion task, as well as a forced-choice recognition task. This conclusion is in accordance with the assumption that perceptual tasks (word completion) are more sensitive to memory in anaesthesia than conceptual tasks of memory (category generation; see Chapter 1). The demonstration of memory for *intraoperative* words by means of forced-choice recognition is quite new (see Chapter 4) and can be explained in terms of Mandler's recognition memory model[1]. The recognition of intraoperative words seems to be based on vague feelings of familiarity. According to Mandler two simultaneous memory processes are involved; first, the 'familiarity' value of an item is retrieved, and at the same time a retrieval process determines whether the target item was originally presented. These two processes seem to result in the correct recognition of an item, in the absence of conscious recollections to the presentation of that item.

Depth of anaesthesia

We argued that the absence of an objective measure of 'depth' of anaesthesia is an issue that has to be addressed in each study into memory in anaesthesia (see Chapters 1, 4, and 5). As long as we are not absolutely sure as to whether anaesthesia is 'adequate' for the entire duration of the operation, we cannot maintain that information-processing during anaesthesia is an unconscious process. In Chapter 1 we distinguished two approaches to this problem, i.e., assessment of intraoperative auditory perception by means of Auditory Evoked Potentials (AEPs) and assessment of the nature (conscious or unconscious) of memory during anaesthesia by means of the Process Dissociation Procedure (PDP)[2,3-5]. PDP is a method from cognitive psychology, to determine the extent to which performance on various memory tasks is mediated by conscious controlled versus automatic processes in memory. The general idea underlying the application of PDP in this context is that 'adequate' anaesthesia is indirectly demonstrated if we can show that unconscious rather than conscious processes underlie memory during anaesthesia. In studies 2 and 3 we applied the exclusion task, a component of PDP, to distinguish between conscious and unconscious contributions to word-completion performance[6]. Both studies revealed a partial exclusion of preoperative words and a failure to exclude intraoperative words. In terms of the logic underlying the exclusion task (see Chapters 4 and 5), exclusion performance on preoperatively presented words indicated both conscious and unconscious influences. Exclusion performance on intraoperatively presented words indicated that unconscious influences were more dominant. However, there is not sufficient basis to quantify in exact figures the extent to which performance on our word-completion task was mediated by conscious, controlled and/or unconscious processes. In other words, we cannot rule out the possibility that memory during anaesthesia was to a certain extent contaminated by conscious influences (see also Chapter 5). Our findings merely provide us with an indication of the dominant type of memory processes, not with the exact extent of conscious and unconscious contributions to memory performance. In our view, future experiments need to include a condition in which all conscious influences can be separated from memory performance in the test phase. The original Process Dissociation Procedure embodies such a condition, i.e., the inclusion task. In an inclusion task subjects are instructed to complete stems with earlier presented words, and if they are unable to do so, to complete with the first word that comes to mind. In this case, both conscious and unconscious influences act in concert because they both serve to *include* earlier presented words. In the exclusion task subjects are told to complete stems with words that were not presented earlier; that is, conscious influences serve to *exclude* or suppress 'old' words. A failure to follow the exclusion instructions reflects unconscious influences. Thus, in the exclusion task conscious and unconscious influences act in opposition. If exclusion (E) performance is subtracted from inclusion (I) performance (I - E) one gets a pure estimation of the conscious contribution to memory performance. For example. If we had used both inclusion and exclusion instructions in study 3, and inclusion of the intraoperative words would have resulted in a mean number of hits of 0.60 and exclusion performance in a mean number of hits of 0.40, then I - E = 0.20. This latter figure would then reflect the *conscious* contribution to word-completion performance[4].

Stimulus characteristics

To determine the experimental conditions under which memory in anaesthesia occurs, we manipulated three different 'stimulus-characteristics' within each experiment. Relevant independent variables were the nature of the stimuli, the number of presentations, and the interval between stimulus presentation and postoperative test. Our results show that all three variables had an effect on unconscious memory processes. These effects are disscussed in the following paragraphs. Study 1 revealed that, relative to previous studies[7,8], less prototypical category exemplars were not reproduced during a postoperative category generation task. In Study 2 word-completion performance was better for common than for less common words. This finding was not replicated in Study 3, nor was there an effect of the 'frequency' of words (common or less common) on forced-choice recognition performance after a 24 h delay in Studies 2 and 3. The finding that common words resulted in larger memory effects than less common words is not in accordance with results from research into implicit memory in *conscious* subjects, which demonstrate an advantage of less common over common words on indirect memory tasks[9,10]. Therefore, our pattern of results suggests that the memory effects found in Studies 2 and 3 were not based on conscious recollections of the intraoperative words because periods of consciousness during anaesthesia would have resulted in an advantage of less common words over common words.

The assessment of the role of 'test-delay interval' (i.e., the interval between learning and test phase) in Study 2 revealed that unconscious memory effects last at least 24 hrs. The intraoperative presentation of words results in the activation of their representations in memory[11]. These representations can remain activated for a longer period, resulting in the demonstration of unconscious memory after a 24-hr delay. This and other findings[12] may be starting-points for further research into the duration of memory effects in anaesthesia studies.

In Studies 1 and 3, patients were exposed to single and multiple presentations of words during anaesthesia. In Study 1 no evidence for memory during anaesthesia was found, and consequently we were unable to demonstrate a possible effect of number of presentations on unconscious memory. Study 3 revealed a word-completion effect after one presentation of words, but not after 30 presentations. The latter finding could not easily be explained and clearly contradicts previous studies[7,8,13-16] in which memory effects were demonstrated after multiple presentations (see also Chapter 4). Therefore, we concluded that the absence of a word-completion effect in Study 3 for the 30x presented words may be spurious. In addition, Study 3 yielded no effect of number of presentations on recognition performance.

Other variables

We were unable to demonstrate a relation between age, gender, estimated pain intensity, and preoperative anxiety on the one hand, and memory performance on the other in either one of the three experiments. Apparently, the memory effects under investigation were not affected by these variables. It is important to note however, that postoperative pain was not measured in our studies while it is conceivable that patients' physical condition shortly after the operation may affect memory performance (see Chapter 1, *Postoperative measurement*). In addition, we used the same standardized, anaesthetic technique across the three studies. The successful replication of the findings of Study 2 in the last study demonstrates that the null finding in Study 1 was not caused by the anaesthetic technique employed. Although we could not demonstrate a relation between preoperative anxiety on the one hand and conscious and unconscious memory on the other, an anecdotal observation in one patient in Study 3 illustrates that preoperative anxiety does seem to affect memory. This patient reported three days postoperatively that he had been having recurrent nightmares about the words that had been presented shortly before surgery. Although the words had been neutral in nature, he unconsciously associated them with the preoperative period during which he had been very scared. Not surprisingly, this patient had been quite anxious relative to the sample mean (STAI-score 54.00, mean 44.6).

Future research

Anaesthetized patients are potentially quite vulnerable to anxiety which is further supported by findings coming from research into cognition and emotion. Recent studies have provided evidence that positive and negative affective states can be induced unconsciously and inhibited by conscious processes[17-19]. This implies that emotional influences may be stronger under unconscious than under conscious conditions. Strong emotional effects may be found under unconscious conditions because emotions are perhaps involved in emergency reactions to which the organism has been biologically prepared. Conscious 'constructions'[1] may mainly serve to diminish the effects of these reactions, in order to prevent negative consequences of emotional reactions when they appear to be 'false alarms'. LeDoux[20] has postulated two distinct neural pathways that may underlie these different processes. His model distinguishes between a short (direct) and a longer pathway, via parts of the neocortex, to the centers involved in the evaluation of stimuli (amygdala and hypothalamus). Several findings suggest that the emotional significance of incoming stimuli may be evaluated unconsciously by the brain, but that consciousness mostly has an inhibitory influence on 'affective processing'[17-19,21]. To test the generality of this pattern future studies might concentrate on the processing of emotionally significant stimuli during general anaesthesia, within ethical standards. Anaesthetics may suppress conscious inhibitory influences and thus undermine the patients' ability to resist adverse emotional effects of surgery.

Many researchers in the area have stressed the importance of getting reliable results and bringing memory in anaesthesia under experimental control[22-25]. The results of Studies 2 and 3 indicate the existence of reliable, replicable effects. We agree with Kihlstrom and Schacter[24] that the next step should be to get reliable results across laboratories and populations. In addition, special attention should be paid to changes in unconscious perception throughout the course of surgery. Information-processing during anaesthesia is a dynamic process that should be assessed accordingly.

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Summary

This thesis describes psychological research into unconscious processes, in particular into memory and perception during general anaesthesia. Chapter 1 provides an overview of recent studies in this area and a discussion of theoretical, methodological, and practical aspects of these studies. Three research methods are described, i.e., administration of therapeutic suggestions, elicitation of postoperative motor responses, and indirect tasks of memory. Studies in which indirect memory tasks were employed seem to provide the best evidence for memory and perception during anaesthesia. The experimental designs and procedures and the interpretation of results of some studies are reviewed and criticised.

Chapter 2 describes the research line of the whole project that consisted of three separate studies (in each study the same anaesthetic technique was employed). These experiments differed with respect to experimental design and procedure. Different relevant experimental variables, which were likely to determine the occurrence of a memory effect, were manipulated within each study. The experiments were conducted as follows; surgical patients undergoing elective procedures under general anaesthesia were presented with words via headphones. Postoperatively, memory for these stimuli was studied by means of simple memory tasks. The specific experimental variables studied were the number of word presentations, the nature of the words (common vs. less common) and of the memory task, and the interval between presentation of stimuli and postoperative task.

Chapter 3 describes a study into the occurrence of memory effects after presentation of less common specimens of word categories (like 'clarinet' for 'musical instruments'). Moreover, words were presented a different number of times. Postoperatively, no memory effect for the words was found, and consequently no effect of number of word presentations could be demonstrated. Chapter 4 describes a study in which two different memory tasks were employed. Both common and less common words were presented during anaesthesia and memory was tested after two delays (4 h and 24 h) with a word completion and a recognition task. Memory for the words was demonstrated immediately after surgery and 24 h later by means of both tasks. The aim of the study described in Chapter 5 was to replicate the findings of the second study. In addition, the effect of number of word presentations on postoperative memory was assessed. Memory for the words presented during anaesthesia was again demonstrated. The final chapter contains an evaluation of the results of the three studies. It is concluded that the circumstances under which memory during anaesthesia occurs can be determined on the basis of these results. The chapter ends with directions for future studies.

Samenvatting

Dit proefschrift is een verslag van experimenteel-psychologisch onderzoek naar onbewuste processen, in het bijzonder onderzoek naar geheugen en waarneming tijdens algehele anesthesie. In hoofdstuk 1 wordt een overzicht gegeven van recente onderzoekingen op dit gebied en worden theoretische, methodologische en praktische aspecten van dergelijke studies behandeld. Een onderscheid wordt gemaakt tussen drie onderzoeksmethoden, te weten aanbieding van therapeutische suggesties, het ontlokken van postoperatieve motorische responsen, en indirecte geheugentaken. Onderzoeken waarbij gebruik is gemaakt van indirecte geheugentaken lijken de meeste evidentie voor geheugen en waarneming tijdens anesthesie te leveren. Bij de opzet, uitvoer en interpretatie van uitkomsten van een aantal studies zijn een aantal kritische kanttekeningen geplaatst.

In hoofdstuk 2 wordt de onderzoekslijn geschetst van het gehele project, dat bestond uit drie deelonderzoeken (telkens met behulp van dezelfde inhalatie-anesthesie) die zich van elkaar onderscheidden in experimentele opzet en uitvoer. Telkens werden binnen de opzet van een onderzoek verschillende relevante experimentele variabelen gemanipuleerd waarvan werd verondersteld dat zij bepalend zouden zijn voor het optreden van geheugeneffecten. Deze experimenten verliepen kortweg als volgt: tijdens verschillende chirurgische ingrepen onder algehele anesthesie werden met behulp van een walkman aan patiënten een aantal woorden aangeboden. Postoperatief werd vervolgens met behulp van eenvoudige geheugentaken (zoals het aanvullen van woordstammen tot volledige woorden) onderzocht of het tijdens de operatie aangeboden materiaal gereproduceerd kon worden. De variabelen die zijn onderzocht waren het aantal aanbiedingen van woorden, de aard van de aangeboden woorden (bekend vs. minder bekend) en van de geheugentaak, en het tijdsinterval tussen aanbieding en test (ofwel het tijdstip waarop de postoperatieve meting plaatsvond).

Hoofdstuk 3 is het verslag van het eerste deelonderzoek, waarin het optreden van een geheugeneffect na aanbieding van minder bekende exemplaren uit woordcategorieën (zoals "klarinet" voor "muziekinstrumenten") werd onderzocht. Bovendien werden deze woorden een verschillend aantal malen aangeboden. Postoperatief werd echter geen geheugeneffect gevonden en dus ook geen effect van aantal aanbiedingen. In hoofdstuk 4 wordt een onderzoek gerapporteerd waarin gebruik is gemaakt van twee andere geheugentaken. Zowel bekende als minder bekende woorden werden tijdens de operatie aangeboden en na twee tijdsintervallen (4 en 24 uur) werd het geheugen onderzocht met behulp van een woordaanvultaak en een herkenningstaak. Met behulp van beide taken werd evidentie gevonden voor geheugen tijdens anesthesie, en deze effecten bleken tot 24 uur na de operatie meetbaar. Het doel van het experiment beschreven in hoofdstuk 5, was het repliceren van de bevindingen uit de vorige studie. Daarnaast werd opnieuw het effect van een verschillend aantal aanbiedingen van woorden bestudeerd. Opnieuw werd met behulp van dezelfde taken geheugen tijdens anesthesie aangetoond. Hoofdstuk 6 tenslotte bevat een evaluatie van de drie deelonderzoeken. Geconcludeerd wordt dat met behulp van deze drie onderzoeken een aantal omstandigheden waaronder geheugen tijdens algehele anesthesie op kan treden, in kaart zijn gebracht. Het hoofdstuk wordt afgesloten met enkele suggesties voor toekomstig onderzoek.

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Curriculum vitae

Annette Bonebakker was born on 1 July 1965 in Goes. After secondary school at the St. Willibrord College in Goes, she studied psychology at the University of Leiden from 1984 to 1989 and graduated in experimental psychology.

She worked as a researcher at the Dutch Institute of Praeventive Health Care-TNO (NIPG-TNO) from 1990 to 1991, and subsequently as a psychology teacher at the Florence Nightingale Institute in The Hague. From 1991 to 1995, she was a research assistant ('Onderzoeker In Opleiding') at the Department of Medical Psychology and Psychotherapy of the Erasmus University Rotterdam, employed by the Dutch Organisation of Scientific Research (NWO). She conducted her research project into memory during anaesthesia at the Department of Anaesthesiology of 'St. Clara' Hospital in Rotterdam.

Since May 1995, she has a position as a consultant psychologist at the Department of Clinical Neurology and Psychology of Psychiatric Centre 'Rosenburg' in The Hague.

Annette Bonebakker werd geboren op 1 juli 1965 te Goes. Na het doorlopen van de HAVO en het VWO aan het St. Willibrord College te Goes begon zij in 1984 met de studie Psychologie aan de Rijksuniversiteit Leiden. In 1989 werd het doctoraalexamen behaald met als afstudeerrichting Psychologische Funktieleer.

Van 1990 tot 1991 was zij werkzaam als wetenschappelijk onderzoeker bij het Nederlands Instituut voor Praeventieve Geneeskunde-TNO te Leiden, ten behoeve van veiligheids- en milieuonderzoek. Aansluitend was zij enige tijd werkzaam als docente psychologie aan het Florence Nightingale Instituut te Den Haag. Van 1991 tot 1995 was zij Onderzoeker In Opleiding (OIO) in dienst van de Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO), gedetacheerd bij het Instituut Medische Psychologie en Psychotherapie van de Erasmus Universiteit Rotterdam. In het kader van deze functie was zij met tussenpozen werkzaam op de afdeling Anesthesiologie van het St. Clara Ziekenhuis te Rotterdam.

Sinds mei 1995 is zij aangesteld als consult-psycholoog bij de afdeling Klinische Neurologie en Psychologie van Psychiatrisch Centrum Rosenburg te Den Haag.