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Analysis of Memory Formation during General Anesthesia (Propofol/Remifentanil) for Elective Surgery Using the Process-dissociation Procedure

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Background: **There have been reports of memory formation during general anesthesia. The process-dissociation procedure has been used to determine if these are controlled (explicit/conscious) or automatic (implict/unconscious) memories. This study used the process-dissociation procedure with the original measurement model and one which corrected for guessing to determine if more accurate results were obtained in this setting.**

Methods: **A total of 160 patients scheduled for elective surgery were enrolled. Memory for words presented during propofol and remifentanil general anesthesia was tested postoperatively by using a word-stem completion task in a process-dissociation procedure. To assign possible memory effects to different levels of anesthetic depth, the authors measured depth of anesthesia using the BIS® XP monitor (Aspect Medical Systems, Norwood, MA).**

Results: **Word-stem completion performance showed no evidence of memory for intraoperatively presented words. Nevertheless, an evaluation of these data using the original measurement model for process-dissociation data suggested an evidence of controlled (C = 0.05; 95% confidence interval [CI] 0.02–0.08) and automatic (A = 0.11; 95% CI 0.09–0.12) memory processes ($P < 0.01$). However, when the data were evaluated with an extended measurement model taking base rates into account adequately, no evidence for controlled (C = 0.00; 95% CI −0.04 to 0.04) or automatic (A = 0.00; 95% CI −0.02 to 0.02) memory processes was obtained. The authors report and discuss parallel findings for published data sets that were generated by using the process-dissociation procedure.**

Conclusion: **Patients had no memories for auditory information presented during propofol/remifentanil anesthesia after midazolam premedication. The use of the process-dissociation procedure with the original measurement model erroneously detected memories, whereas the extended model, corrected for guessing, correctly revealed no memory.**

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ANESTHESIA is commonly described as a state characterized by hypnosis, analgesia, immobility, and amnesia. Depth of hypnosis is regarded as a continuum from light sedation to a comatose state. With increasing depth of hypnosis, the ability of the brain to process information and its ability to form new memories are diminished. During surgical depth of hypnosis, patients expect unconsciousness and the absence of memory formation.

Nevertheless, there have been reports of controlled (synonymously used: explicit, conscious) as well as automatic (implicit, unconscious) memory processes as a result of learning under general anesthesia.[1,2] Controlled memory processes can be characterized in terms of intentional or conscious recollection of previous information, whereas the notion of automatic memory processes refers to changes in performance or behavior that occur without reference to previous learning episodes.[3]

A number of studies have attempted to investigate memory formation under anesthesia and have revealed contradictory results,[4–8] some of which may have been caused by differences in methodology, anesthetic regimen, or time interval between anesthesia and postoperative testing.

The process-dissociation procedure,[9] often in combination with word-stem completion, has increasingly been used in anesthesia research for assessing controlled and automatic memory processes within a single task. The procedure consists of two conditions (inclusion and exclusion condition). In the inclusion condition, patients are typically instructed to complete word stems with the first word that comes to mind. Correct completion of a word stem to a target word, *i.e.*, a word which was presented earlier, is called a hit and is assumed to be evidence of the joint operation of controlled and automatic memory processes. In this condition, one cannot decide whether correct completions result from controlled or automatic memory processes. In the exclusion condition, patients are to avoid completing word stems with the first word that comes to mind and to use another word instead. If completion rate is below the base rate (*i.e.*, the probability of correctly completing nonpresented [distractor] words), then, this is assumed to be evidence of controlled memory processes. In this context, the question has been raised whether postoperative automatic effects of memory for intraoperative events is the result of short periods of awareness under

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anesthesia or of truly automatic (unconscious, implicit) memory processes.[10,11]

Unfortunately, there are differences among studies with respect to both the pattern of results and the measurement models used to evaluate raw word-stem completion performance. For instance, there is evidence of controlled, but not automatic, memory processes when using a nonevaluated *ad hoc* measurement model with unknown properties[12] and of automatic, but not controlled, memory processes when using Jacoby's original measurement model[13] after exposure to words during anesthesia.

Available measurement models differ in whether base rate performance and guessing are taken into account; if guessing is taken into account, models differ in whether they have or have not been shown to be empirically adequate. It is well-known that the adequacy with which base rates are taken into account in a process-dissociation measurement model may have considerable influences on the pattern of results. Given that only the extended measurement model suggested by Buchner[14] yielded valid results in previous systematic evaluation studies, we thought it important to reanalyze previously published memory under anesthesia or sedation data.[8,12,13,15]

The purposes of the current study were (1) to assess possible memory for intraoperative events and (2) to compare two principal measurement models (Jacoby's original measurement model and an extended measurement model) for data obtained using the process-dissociation procedure[9,14] with the goal to clarify some of the uncertainties just mentioned.

Materials and Methods

Patients

One hundred sixty patients scheduled for minor urological, gynecological, general, or orthopedic surgery were enrolled in the study after approval of the institutional review board of the Charité - Universitaetsmedizin Berlin, Berlin, Germany and written informed consent. Criteria for exclusion were neurologic or psychological disorders, history of abuse of alcohol or illegal drugs, psychoactive medication, and hearing deficits.

Memory Testing and Analysis

To assess whether patients exhibit memory for auditory words presented intraoperatively, a postoperative word-stem completion task was used. If the word-stem completion rate was above the base rate (*i.e.*, the probability of correctly completing nonpresented [distractor] words), then this indicates memory for intraoperative events. The process-dissociation procedure was used to enable decomposition of any memory for intraoperatively presented words into controlled and automatic components. In addition, two different process-dissociation measurement models, one taking guessing into account, were used to be able to determine how accurately these models measure memory.

Forty two-syllable target words were chosen from a list of five- to six-letter German words created for word-stem completion tasks[16] according to the following criteria: (1) spontaneous completion of the word stem with the target word by the general population was about 20–30%; (2) there had to be at least four possible completions to German five- to six-letter nouns in addition to the target word; (3) the degree of spontaneous association with threat or familiarity of the body-related nouns had to be low (score < 3).[17]

Words were digitally recorded on a notebook computer and played to the patients *via* closed headphones after the induction of general anesthesia at about 75 dB(A), *i.e.*, the sound pressure level with frequencies being weighted according to the frequency-specific sensitivity of the human ear for low to medium sound levels. Each patient was presented with 20 randomly chosen words. Each single word was repeated 40 times (with 2.5 s between the repetitions) before the next target word was presented.

The BIS® XP monitor (Aspect Medical Systems, Norwood, MA) was used to record anesthetic depth, but anesthesiologists were blinded to the monitor. Settings for the BIS® XP monitor were: 15-s smoothing period, notch filter on. Electrode impedance was kept below 5 kΩ. Bispectral index (BIS) readings were used retrospectively to be able to relate possible differences in memory performance to anesthetic depth during the time of word presentation.

Memory testing was performed 6–24 h postoperatively depending on the time of the end of the operation. Patients responded to a short structured interview (after Brice *et al.*[18]) and were then instructed to complete word stems to form five- to six-letter, two-syllable German words as required within the process-dissociation procedure introduced by Jacoby.[9]

Process-dissociation Procedure and Process-dissociation Measurement Models

In the inclusion condition of the process-dissociation procedure, patients were asked to complete each word stem to a word presented during the intraoperative period, if possible. With every measurement – the measurement of memory in the current case – certain assumptions must necessarily be made. Frequently, these assumptions are not discussed explicitly. One advantage of the process-dissociation approach is that the assumptions are explicitly stated in what can be called a measurement model. For instance, target completions in the inclusion condition are assumed to occur as the result of the joint operation of controlled and automatic memory processes. The measurement model specifies exactly how this joint operation is assumed to occur. For in-

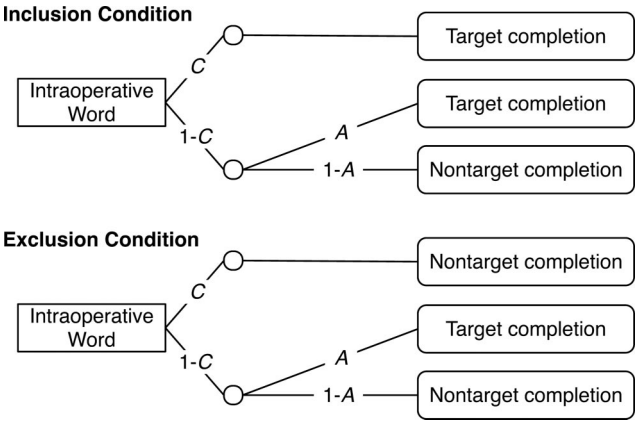

Fig. 1. The original measurement model as suggested by Jacoby (see the subsection entitled "Process-dissociation Procedure and Process-dissociation Measurement Models" in the Material and Methods section for details). *A* = probability of target completion based on automatic memory processes; *C* = probability of target completion based on controlled memory processes.

stance, in the original measurement model suggested by Jacoby (fig. 1), target completion based on controlled memory processes (recollections of words from the intraoperative period in our case) is assumed to occur with probability *C*. In the absence of controlled recollections (which occurs with probability 1 – *C*), automatic memory processes may lead to target completions with probability *A*. Thus, the probability of target word completions in the inclusion condition, TI, is given by

$$TI = C + (1 - C) * A, \quad (1)$$

where *C* and *A* are assumed to be stochastically independent.

In the subsequent exclusion condition, patients were asked to reject a word as a completion to a word stem if they recognized the word as coming from the intraoperative period and to use another word meeting the criteria of the instructions. In the original measurement model suggested by Jacoby, this type of recollection-based nontarget completion is assumed to occur as a result of controlled memory processes which, again, are assumed to occur with probability *C*. If this type of target word rejection were not possible because no suitable word was recollected from the intraoperative period, patients were to use the first word that came to mind. As in the inclusion condition, in the absence of controlled recollections (which occurs with probability 1 − *C*), automatic memory processes may still lead to target completions with probability *A*. Thus, the probability of target word completions in the exclusion condition, TE, is given by

$$TE = (1 - C) * A. \quad (2)$$

Plugging (2) into (1) yields

$$TI = C + TE, \quad (3)$$

It follows that the probability of a controlled memory process, *C*, may be determined as the difference between target completions in the inclusion and exclusion conditions, that is,

$$C = TI - TE. \quad (4)$$

It also follows that the probability of an automatic memory process, *A*, can be determined as

$$A = TE/(1 - C). \quad (5)$$

Note that in this original measurement model it is assumed that target word completions occur exclusively as a result of memory processes (controlled as represented by parameter *C* or automatic as represented by parameter *A*). Mere guessing is assumed not to occur at all. As a result, base rates are completely ignored by this measurement model. This assumption is obviously questionable. Therefore, we also used an extended measurement model which does take guessing and, hence, base rate performance into account (see fig. 2).[14] The extended measurement model is similar to the original measurement model but allows for the additional possibility that target completions to intraoperatively pre-

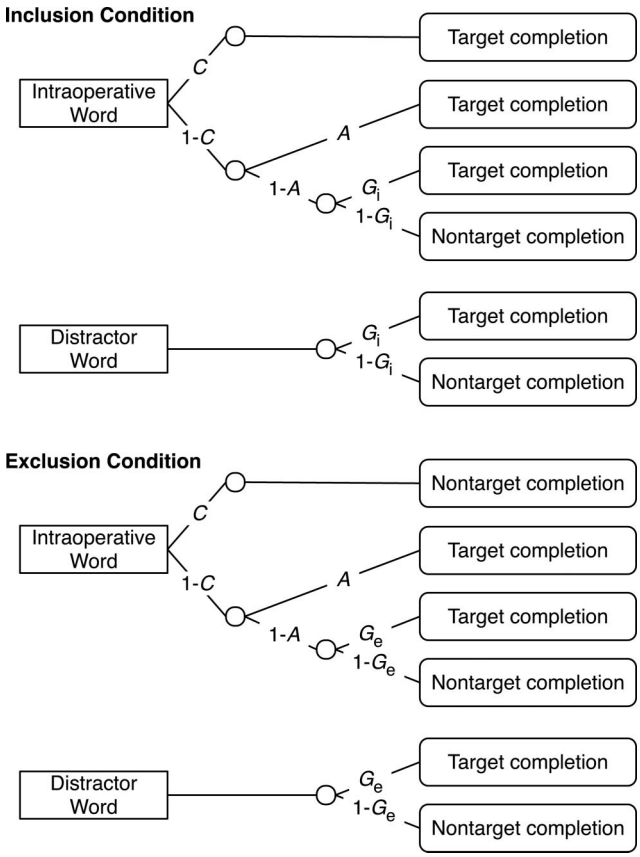

Fig. 2. Graphical illustration of the extended measurement model (see the subsection entitled "Process Dissociation Procedure and Process Dissociation Measurement Models" in the Material and Methods section for details). *A* = probability of target completion based on automatic memory processes; *C* = probability of target completion based on controlled memory processes; G_i = conditional probability of guessing-based target word completions in the absence of controlled or automatic memory processes in the inclusion condition.

sented words that are neither recollected (with probability $1 - C$) nor supported by automatic memory processes (with probability $1 - A$) may still be arrived at by pure guessing. Guessing-based target word completions in the absence of controlled or automatic memory processes are assumed to occur with conditional probability G_i in the inclusion condition and with conditional probability G_e in the exclusion condition. Nontarget completions occur with conditional probabilities $(1 - G_i)$ and $(1 - G_e)$ in the inclusion and exclusion conditions, respectively. The extended model also assumes that completions to distractor words, that is, words that were not presented during anesthesia, can only be arrived at by guessing with probability G_i (in the inclusion condition) and with probability G_e (in the exclusion condition). Importantly, it has already been shown empirically in a series of controlled experiments that the extended measurement model is superior to the original measurement model because it takes guessing and, hence, base rates into account adequately.[14]

Of the 20 words presented during anesthesia, 10 words were randomly selected and defined as targets for the inclusion condition. The remaining 10 words presented during anesthesia were defined as targets for the exclusion condition. At test, word stems of the 10 target words in combination with 10 word stems selected randomly from the words that had not been presented earlier (distractors) were presented in either test condition, *i.e.*, a total of 40 word stems. Word stems were presented to the patients auditorily *via* headphones and synchronously in black letters on a white notebook computer screen. The sequence of words was randomized for each patient. Word stems were generated by digitally removing the ending from the original words that had been recorded for the intraoperative presentation.

Anesthetic Regimen

Patients were premedicated orally with 0.1 mg/kg midazolam syrup. General anesthesia was induced with a bolus application of 1–2 μg/kg fentanyl or 0.1–0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil infusion followed by 2–3 mg/kg propofol as a bolus application *via* a Fresenius® Base Primea syringe pump (Fresenius Kabi, Bad Homburg, Germany) or a Alaris® CC syringe pump (Cardinal Health, Rolle, Switzerland), respectively. Patients were given 0.1–0.15 mg/kg cisatracurium for muscle relaxation. For two patients, 1 mg/kg succinylcholine was used for neuromuscular blockade.

Anesthesia was then maintained as a total intravenous anesthesia with $6–8 \text{ mg} \cdot kg^{-1} \cdot h^{-1}$ propofol and $0.1–0.5 \mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil *via* the Fresenius Base Primea® syringe pump (Fresenius Kabi) or the Alaris® CC syringe pump (Cardinal Health). After the end of anesthesia, the endotracheal tube was removed, and patients were transferred to the recovery room.

Literature Analysis

Articles using the process-dissociation procedure to assess memory for information presented during anesthesia were retrieved by a PubMed search. Only those studies were selected for which the inclusion and exclusion word-stem completion frequencies could be reconstructed from the published sample data.‖

Statistical Analysis

Memory performance was assessed in two steps. First, observed word-stem completion performance was assessed directly and separately for the inclusion and exclusion conditions by using paired-sample *t* tests. Second, the process-dissociation data were analyzed using Jacoby's original measurement model[9] and the extended measurement model suggested by Buchner *et al.*[14] in a multinomial modeling approach. This statistical approach may still be somewhat unfamiliar to researchers outside areas such as memory research,[19] but it has a number of advantages over the more traditional general linear model approach,[14] which is why we use it here. In essence, a measurement model such as Jacoby's original measurement model is fitted to sample data, and the goodness-of-fit of model and data are tested using the goodness-of-fit statistic G^2, which is asymptotically chi-square distributed with degrees of freedom indicated in parentheses.

In the current case, the measurement models illustrated in figures 1 and 2 were fitted to the empirical target and nontarget word-stem completion frequencies obtained in the current study using the AppleTree program (Axel Buchner, Düsseldorf, Germany).[20]

In this way, sample estimates for all model parameters (C and A of the original measurement model; C, A, G_i, and G_e for the extended measurement model) were simultaneously computed in an iterative procedure such that the models fit the data optimally. For instance, the sample estimate for parameter C (representing the probability of controlled memory processes) was determined to be 0.05 when the original measurement model was used to evaluate the current data. AppleTree also computes the 95% CI for each parameter estimate. For instance, the confidence interval for the estimate of parameter C just mentioned was 0.02–0.08.

In multinomial models such as the original and extended measurement models, statistical tests can be performed directly on the model parameters. For instance, the test of the hypothesis that there were no controlled memory processes would proceed as follows. First, the complete original measurement model as illustrated in figure 1 would be fitted to the empirical data presented in Supplemental Digital Content 1 (see table, which contains the empirical target and nontarget completion frequencies in

‖ Available at: http://www.ncbi.nlm.nih.gov/pubmed/. Accessed October 15, 2008.

the current experiment, http://links.lww.com/A1448). As a result, one gets sample estimates for parameters C and A. Second, to test whether controlled memory processes are involved in task performance, the original model would be restricted by setting the parameter representing controlled memory processes to zero ($C = 0$). This restriction implements the assumption that no controlled memory processes are involved in target completion performance. In statistical terms, this restriction generates one degree of freedom because parameter C already has a value (0 in this case) and therefore no longer needs to be estimated from the sample data. Third, if the restricted model fits the data, then this is indicated by a G^2 value that is associated with $P > 0.05$ (provided the conventional level of $\alpha = 0.05$ is adopted). More specifically, for the model with the restriction that $C = 0$, all $G^2(1)$ values smaller than the critical $\chi^2(1) = 3.84$ would be associated with $P > 0.05$, which would indicate that this model (and its implied assumption of $C = 0$) is compatible with the data. In this case, we would have to conclude that controlled memory processes for intraoperatively presented words were not involved in word-stem completion performance. In contrast, if the model with the restriction that $C = 0$ does not fit the data, then this is indicated by a G^2 value that is associated with $P < 0.05$. All $G^2(1)$ values larger than the critical $\chi^2(1) = 3.84$ would be associated with $P < 0.05$. In this case, we would have to conclude that controlled memory processes for intraoperatively presented words *were* involved in word-stem completion performance.

Results

Patient Characteristics

After enrollment, we excluded 41 of the patients for the following reasons: failure of the personal computer notebook, word presentation program, or recording of the data (6 patients); use of anesthetic drugs other than those allowed by the protocol (3 patients); administration of sedative drugs other than the preoperative premedication before anesthesia or before postoperative memory testing (11 patients); interruption of investigation due to interference with procedures in the operating room (1 patient), unexpected prolongation of anesthesia due to hypothermia (1 patient); suspicion of unadmitted abuse of alcohol (1 patient); postoperative testing not possible within 24 h postoperatively due to early discharge or patient's indisposition or refusal to perform the postoperative testing (13 patients); end of surgery before the end of word presentation (5 patients).

A total of 119 patients were included in the final sample (77 women, 42 men). Mean patient age in the final sample was 53 ± 14.5 yr, height was 169 ± 7.9 cm, and weight was 73.9 ± 16.3 kg. Median duration of surgery was 128 min (25th–75th percentile 88–201 min), and mean duration of intraoperative word presentation was 27 min.

For the induction of anesthesia, patients received a fentanyl bolus of 2.26 ± 0.69 μg/kg (99 patients, mean ± SD) or remifentanil infusion (20 patients), resulting in an effect site concentration of 5.82 ± 1.71 ng/ml at the time of intubation. For maintainance, propofol and remifentanil were administered *via* manually controlled infusion. The resulting effect site concentrations were 2.88 ± 0.65 μg/ml for propofol and 5.08 ± 2.72 ng/ml (mean ± SD) for remifentanil during intraoperative word presentation. Two patients received a single bolus of fentanyl at induction due to a relatively short operative procedure.

Memory Performance

No patient reported having memory for intraoperative events in the short structured interview (after Brice *et al.*[18]). Similarly, word-stem completion performance indicated that there was no memory for intraoperatively presented words. In the inclusion condition, the mean target completion rate (0.15 ± 0.10, mean ± SD) was not significantly different from the base rate (0.16 ± 0.13; $t^{118} = -0.54$; $P = 0.59$). The target completion rate in the exclusion condition was 0.1 ± 0.11 and thus lower than the inclusion condition target completion rate, but not significantly different from the exclusion condition base rate (0.1 ± 0.09, mean ± SD; $t^{118} = -0.35$; $P = 0.73$).

If one were only interested in memory for intraoperatively presented auditory information as implemented here, then one could stop analyzing the current data because we already know now that there is no evidence of memory. However, as stated in the introduction, one of the purposes of this study was to demonstrate that the results obtained using the process-dissociation procedure critically depend on the type of measurement model that is used for data analysis. As will become clear in the next paragraph, this demonstration is in fact fortified considerably by the fact that we already know that there is no evidence for memory processes in the current data.

The analyses of these data by using process-dissociation measurement models are presented in table 1. When analyzed with Jacoby's original measurement model (fig. 1), the parameter estimates for both C and A were clearly above zero. This difference from zero was statistically significant, as can be seen from the fact that the model with the restriction that $C = 0$ did not fit the data, and the same was true for the model with the restriction that $A = 0$ (the test statistics for these hypothesis tests are presented in the row immediately below the confidence intervals in table 1).

In contrast, the parameter estimates for both C and A drop to zero when raw word-stem completion data were analyzed by using the extended measurement model,

Table 1. Analyses of Word-stem Completion Data Using Two Different Measurement Models

	Original Measurement Model		Extended Measurement Model			
	C	*A*	*C*	*A*	*Gi*	*Ge*
Parameter estimate (CI)*	0.05 (0.02 to 0.08)	0.11 (0.09 to 0.12)	0.00 (–0.04 to 0.04)	0.00 (–0.02 to 0.02)	0.15 (0.13 to 0.17)	0.10 (0.08 to 0.11)
$G^2(1)$ for test of equality with zero	13.84†	1455.36†	0.00	0.00		

Analyses of word-stem completion data obtained in the process-dissociation procedure using Jacoby's original measurement model[9] and the extended measurement model.[14] Sample response frequencies (Supplemental Digital Content 1, http://links.lww.com/A1448) were submitted to a multinomial model-based analysis.

* Lower and upper limits of the 95% confidence interval (CI). † $P < 0.01$.

A = probability of target completion based on automatic memory processes; C = probability of target completion based on controlled memory processes; G_i = conditional probability of guessing-based target word completions in the absence of controlled or automatic memory processes in the inclusion condition; G_e = conditional probability of guessing-based target word completions in the absence of controlled or automatic memory processes in the exclusion condition.

which is where they should be, given that there is no evidence of memory in the inclusion and exclusion data. The statistical tests reported in the right half of table 1 show that both *C* and *A* are no longer significantly different from zero.

In a final step, we analyzed whether there were any differences in the parameters representing memory processes as a function of (1) the depth of anesthesia and (2) anesthetic regimen. For the first analysis, patients with medians of BIS of 39.5 or more and BIS 39.4 or less during word presentation were retrospectively assigned to the high (median BIS = 42, n = 81) and low (median BIS = 28.2, n = 38) BIS groups, respectively. There were no differences between these groups in any of the parameters of the extended measurement model (*C*: 0.01 *vs.* 0.00; *A*: 0.01 *vs.* 0.00; G_i: 0.14 *vs.* 0.16; G_e: 0.09 *vs.* 0.10 for the high *vs.* low BIS groups, respectively). The extended model with the restriction that parameters *C*, *A*, G_I, and G_e were equal in the two BIS groups fitted the data perfectly (G^2 (4) = 1.24, $P = 0.87$). For the second analysis, patients receiving fentanyl (n = 99) were contrasted to patients not receiving fentanyl (n = 20). There were again no differences between these groups in any of the parameters of the extended measurement model (*C*: 0.00 *vs.* 0.00; *A*: 0.00 *vs.* 0.00; G_i: 0.18 *vs.* 0.15; G_e: 0.10 *vs.* 0.10 for the fentanyl *vs.* no fentanyl groups, respectively). The extended model with the restriction that parameters *C*, *A*, G_I, and G_e were equal in the two BIS groups fitted the data perfectly (G^2 (4) = 2.05, $P = 0.73$).

Reanalyses of Published Data

A total of four studies were identified that allowed a reanalysis of process-dissociation data. The characteristics of these studies are given in table 2. The results of these reanalyses are presented in table 3. For the first three of the four studies characterized in table 2, the published results suggest that controlled memory processes were involved in task performance in all cases and that automatic memory processes were involved in task performance in one case. When these data were analyzed by using the extended measurement model, the evidence of controlled and automatic memory processes disappeared completely. For the fourth study in table 2, the conclusions about the results did not change when the extended measurement model replaced the original model, but the estimate for parameter *A* representing automatic memory processes was reduced substantially from 0.15 to 0.04.

A few comments on the individual studies seem necessary: (1) In the study by Stapleton and Andrade, the base rate was simply subtracted from the estimate of the parameter representing automatic memory processes. To our knowledge, such a model has never been systematically evaluated so that the effects of this *ad hoc* adjustment are unknown. However, please note with respect to parameter *A* of this *ad hoc* model that parameters represent probabilities that cannot become negative by definition. The fact that the authors report a negative probability for their measure of automatic memory processes indicates the inadequacy of their measurement model and data evaluation procedure. What is more, parameter *C* of this model is just the parameter of Jacoby's original measurement model and thus has all the problems of parameter *C* of that model. (2) Kerssens *et al.* did not explicitly state which measurement model they used. However, they report and interpret the fact that the hit rate in the inclusion condition was significantly different from the hit rate in the exclusion condition. This difference is identical to parameter *C* of Jacoby's original measurement model. We report an analysis of their data using this model. (3) Lubke *et al.* report no test statistics or *P* values. The authors report to have used the extended measurement model, but it is not clear which statistical method they used to arrive at their conclusion that this value was different from zero. (4) Iselin-Chaves *et al.* report in their table 2 an estimate of $C = 0.04$. This does not fit with the fact that they also report equal target completion rates of 0.15 for the inclusion and exclusion conditions, resulting in $C = 0.15 - 0.15 = 0$. We never-

Table 2. Characteristics of the Published Studies Using the Process Dissociation Procedure during Anesthesia

First Author	n	Anesthetic Regimen	Premedication	Anesthetic Depth/BIS
Stapleton[12]	72	Infusion mixture of propofol/alfentanil: (1) 9 mg/ml propofol and 0.05 mg/ml alfentanil in 36 patients; (2) 8 mg/ml propofol and 0.1 mg/ml alfentanil in 36 patients after a change in hospital policy unrelated to the study.	1 g of paracetamol 30 min before surgery.	Maintenance of a level of sedation and analgesia "such that patients were comfortable but opened their eyes in response to command."
Lubke[8]	24	Rapid-sequence induction: 4 mg/kg thiopental and 100 mg of succinylcholine. Maintenance: 50% N_2O/O_2 with 0.2% isoflurane (end-tidal concentration before delivery). After delivery: 70% N_2O with 0.2% isoflurane (end tidal) and 0.1–0.15 mg/kg morphine.	"No benzodiazepine/scopolamine or exogenous central nervous system active agents administered in the 6 h before surgery."	BIS 76.3 ± 3 (A1000 Monitor*) with a two-channel referential montage.
Kerssens[15]	56	TCI of propofol: Induction 6 μg/ml, bolus 20 μg/kg alfentanil, 1 mg/kg suxamethonium, 0.1 mg/kg vecuronium bromide. Propofol plasma concentration was targeted to BIS (60–70) for the remainder of the presurgical study period, and word presentation started as soon as BIS was above 60.	None	BIS 64 ± 3 (A1000 monitor) with a two-referential montage.
Iselin-Chaves[13]	48	Induction: opiate and a hypnotic. Succinylcholine or nondepolarizing agents were used to facilitate tracheal intubation. Maintenance: "opiate, a mixture of O_2–air or N_2O, a nondepolarizing agent if necessary, and a hypnotic (halogenated agent or propofol). A regional anesthesia might be associated with the general anesthesia. Induction and maintenance of anesthesia were at the discretion of the responsible anesthesiologist."	None	BIS 49 ± 9 (A-2000 monitor).

* Aspect Medical Systems, Norwood, MA.

BIS = bispectral index; N_2O = nitrous oxide; O_2 = oxygen; TCI = target-controlled infusion.

theless report $C = 0.04$ as is reported in the original study. See Supplemental Digital Content 2 (see table, which shows the empirical target and nontarget completion frequencies underlying the reanalyses presented here, http://links.lww.com/A1449).

Discussion

We showed that patients receiving adequate to deep propofol/remifentanil total intravenous anesthesia according to the values displayed by the BIS did not exhibit controlled (explicit/conscious) or automatic (implicit/unconscious) memory as a result of learning during elective surgery. As such, this finding stands in contrast to a variety of reports of memory formation under general anesthesia,[4,7,8,10,15,21] but it is in line with other findings.[5,6]

However, as we have shown, our results are very similar to those obtained in related studies using the process-dissociation procedure[8,12,15] when an adequate measurement model for the evaluation of process-dissociation data is used. An adequate measurement model is one that has been shown empirically to take guessing and base rates into account. This is the case for the extended measurement model.[14] In contrast, the original measurement model suggested by Jacoby[9] completely ignores guessing and base rates. As we have shown here (table 1) and elsewhere,[14] this leads to serious distortions in the estimates of the parameters that are assumed

Table 3. Analyses of Process-dissociation Procedure Data from Published Studies

	Parameter Estimates as Published with the Original Studies		Extended Measurement Model			
	C	*A*	*C*	*A*	G_i	G_e
Stapleton[12] (intraopertative presentation)						
Parameter estimate	0.06‡	–0.03	0.03	0.00	0.32	0.29
Confidence interval*			–0.03 to 0.09	–0.05 to 0.05	0.28 to 0.35	0.26 to 0.32
$G^2(1)$ for test of equality with zero			0.95	0.00		
Lubke[8]						
Parameter estimate	0.11†	0.00	0.10	0.00	0.30	0.27
Confidence interval*			–0.02 to 0.23	–0.10 to 0.10	0.24 to 0.37	0.21 to 0.33
$G^2(1)$ for test of equality with zero			2.56	0.00		
Kerssens[15]						
Parameter estimate	0.05†	0.23‡	0.04	0.00	0.25	0.24
Confidence interval*			–0.03 to 0.10	0.04 to 0.05	0.21 to 0.28	0.21 to 0.27
$G^2(1)$ for test of equality with zero			1.24	0.00		
Iselin-Chaves[13] (anesthesia group)						
Parameter estimate	0.04	0.16‡	0.00	0.04	0.12	0.11
Confidence interval*			–0.05 to 0.05	0.01 to 0.08	0.09 to 0.15	0.08 to 0.14
$G^2(1)$ for test of equality with zero			0.00	6.72‡		

Published estimates of the probabilities of controlled and automatic memory processes are presented in the first two data columns under *C* and *A,* respectively. The subsequent columns contain the estimates for controlled and automatic memory processes as well as guessing processes when the data were analyzed using the extended measurement model.[14] Sample response frequencies were reconstructed from the original publications and were submitted to a multinomial model-based analysis.

* Lower and upper limits of the 95% confidence interval (CI). † $P \leq 0.05$. ‡ $P \leq 0.01$.

A = probability of target completion based on automatic memory processes; *C* = probability of target completion based on controlled memory processes; G_i = conditional probability of guessing-based target word completions in the absence of controlled or automatic memory processes in the inclusion condition; G_e = conditional probability of guessing-based target word completions in the absence of controlled or automatic memory processes in the exclusion condition.

only to represent memory processes but are in fact contaminated by guessing processes. Most interestingly, we have shown with our own data that by using the original measurement model one may obtain "evidence" of controlled and automatic memory processes, even in situations in which there is no contribution of memory at all. One consequence of using the extended measurement model is that this spurious evidence of memory processes disappears completely.

As mentioned in the results section, if there are clearly no differences between the target and distractor completion rates in both the inclusion and the exclusion conditions of studies using the process-dissociation procedure, then one may stop analyzing the data and conclude that no memory is involved in task performance. However, the situation will often not be as unambiguous as it is in the current study. Instead, there may be slight differences between target and distractor completion rates in combination with more or less pronounced differences between the inclusion and exclusion completion rates (see, for instance, the studies for which we present reanalyses in table 2), such that one may wonder whether these small differences together might be reason to assume that memory was involved in task performance. In these situations, our recommendation clearly is to use the extended measurement model and not the original measurement model. This is so because, as we have shown in the current paper, use of the original model may easily lead to an overestimation of the contribution of memory-based processes and even to the erroneous conclusion that memory was involved when it in fact was not, whereas, even for this extreme situation, the extended measurement model leads to the correct conclusion that memory was not involved.

Another consequence of using the extended measurement model to analyze process-dissociation data is that previous inconsistencies in the published literature vanish almost completely. For the first three of the four studies characterized in table 2, it turns out that there is no evidence of any involvement of controlled or automatic memory processes. For the fourth study in table 2, the conclusions about the results did not change when the extended measurement model was used, but the estimate for parameter *A* representing automatic memory processes was substantially re-

duced from 0.15 to 0.04. Even here, the contribution of memory processes has been very seriously overestimated as a result of the fact that the original measurement model was used to evaluate the data.

An additional consideration concerns the depth of anesthesia, which was rather deep in our study (median BIS = 32.5). This level of anesthesia corresponds to that present during the display of a subgroup of words for which Iselin-Chaves *et al.* reported very little evidence of automatic memory processes when compared to subgroups with lighter anesthesia (see their fig. 1). If we add to this that using the more adequate extended measurement model would probably lead to an estimate of the contribution of memory to performance in this subgroup that was even lower (perhaps even zero), it becomes reasonable to assume that the deep level of anesthesia in our study explains the lack of memory contributions to postoperative word-stem completion performance.

In contrast to other studies, the patients in our study received midazolam for oral premedication. The use of a midazolam premedication may be one possible explanation for the lack of memory formation in this study. Midazolam is known to produce anterograde amnesia.[22] Current knowledge suggests an effect of midazolam on explicit processes rather than on implicit processes.[23–25] Nevertheless, there have been reports of memory formation and even conscious awareness after midazolam or benzodiazepine premedication or coinduction especially in clinical routine settings.[1,26,27] An explanation for this may be the relatively short duration of action of a single dose of midazolam.

Additional considerations concern the study protocol, as it is known that patients under different conditions are at a higher risk of awareness. This has been shown for emergency procedures, cardiac surgery, or obstetric surgery.[28] Moreover, further studies are needed to compare process-dissociation procedure data obtained under anesthesia with intravenous and volatile anesthetics.

In essence, our results show no evidence of the contributions of controlled or automatic memory processes to word-stem completion performance when the target words were presented during relatively deep levels of anesthesia. This seems to fit with earlier findings. Moreover, we showed that the choice of the measurement model is critical when using the process-dissociation procedure. Using an inadequate model such as that of Jacoby, which fails to adequately account for base rates, may very easily lead to spurious "evidence" of memory formation during anesthesia. The extended measurement model should be used instead.

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