Recovery of memory after general anaesthesia: clinical findings and somatosensory evoked responses

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Background. Mid-latency somatosensory evoked responses are used to monitor the integrity of the sensory pathways intra-operatively. They can quantify the effects of anaesthetics on the central nervous system. Mid-latency auditory evoked responses have been related to cognition during anaesthesia, but there are no detailed studies using median nerve somatosensory evoked responses (MnSSER).

Methods. We studied 49 patients during recovery from general anaesthesia (isoflurane/nitrous oxide or propofol) to assess implicit and explicit memory function in relation to mid-latency MnSSER. The MnSSER recordings were made before anaesthesia, during steady-state anaesthesia, and at the end of the recovery period. The patients were interviewed 24 h later about their memory for the immediate wake up phase. Statistical analysis was by multivariate analysis of variance.

Results. Out of 49 patients, 23 recalled the recovery period, 11 had implicit memory for an object shown to them during the recovery period, and 15 did not have any memory for the recovery period. At RECOVERY the patients with recall had significantly shorter MnSSER latencies N45 and P50 and inter-wave conduction times LatN35 – LatP45 than patients without memory (P<0.05).

Conclusions. We conclude that MnSSER components warrant further investigation for studying the effects of anaesthetic drugs on cognitive function.

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Although large clinical surveys report explicit awareness in less than 0.2% of patients during anaesthesia for general surgery, this adverse-event is a great concern, because the patients may be permanently affected by the experience.1 Recall of intra-operative events will presumably occur if information processing is not adequately blocked by anaesthetics. During anaesthesia there is no clinical sign indicating the likelihood of persistent memory, so indirect signs are used to judge the state of the patient. Measurements from the spontaneous and the evoked electroencephalogram (EEG) have been introduced to assess cerebral function during general anaesthesia. The bispectral index, a computer-derived parameter of the spontaneous EEG, and the auditory evoked response (AER), may allow assessment of persistent memory during anaesthesia,2 but there is no standard means to assess memory during anaesthesia.

Median nerve somatosensory evoked responses (MnSSER) have not been studied in relation to memory during anaesthesia. However, MnSSER can be part of standard monitoring for neurosurgical, vascular, or orthopedic procedures, when nervous structures are at risk during the operation. Therefore, it is interesting to find out if they provide further information about cerebral signal processing other than information about the integrity of the sensory pathway. MnSSER can indicate cortical arousal during surgical stimulation.3 We do not know if they indicate the analgesic component during anaesthesia, whereas the AER may reflect the hypnotic component.4,5 We have shown, that MnSSER changes in relation to clinical awakening during
recovery from general anaesthesia. Theoretically, MnSSER could be used for monitoring during anaesthesia, if AER recording was not practical, for example as a result of hearing problems in patients.

We set out to describe memory and mid-latency MnSSER during recovery from general anaesthesia. The recovery period was chosen because the incidence of persistent memory during surgical anaesthesia is supposed to be low. The present investigation describes memory performance, while recovery of MnSSER with decreasing anaesthetic dose has been published previously.6

**Patients and methods**

**Patients**

With approval from the local ethics committee and written informed consent, we prospectively studied 49 female patients (mean 41 (SD 12) [range 18–67] yr, 1.67 (0.08) m, 67.9 (14) kg, ASA I–II), about to have elective gynaecological operations of about 1 h. We excluded patients with neurological diseases. No patients were taking centrally acting drugs.

**Anaesthesia**

All patients were given midazolam 7.5 mg orally as a premedication 45 min before anaesthesia. According to their date of birth, patients were allocated to two different anaesthetic treatments. In one group, anaesthesia (n=20) was induced with propofol 2 mg kg\(^{-1}\), sufentanil 0.5 µg kg\(^{-1}\), and vecuronium 0.1 mg kg\(^{-1}\). After tracheal intubation, anaesthesia was maintained with propofol 8 mg kg\(^{-1}\) h\(^{-1}\). Supplementary doses of sufentanil 0.25 µg kg\(^{-1}\) were given as necessary. The patients in the other group (n=29) received etomidate 0.3 mg kg\(^{-1}\), fentanyl 1.5 µg kg\(^{-1}\), and vecuronium 0.1 mg kg\(^{-1}\) for induction of anaesthesia. After tracheal intubation, anaesthesia was with isoflurane 0.6% (end-tidal) in nitrous oxide/30% oxygen supplemented with doses of fentanyl 0.5 µg kg\(^{-1}\). At the end of surgery, when median evoked responses had been recorded during anaesthesia, the administration of the anaesthetics was stopped and 100% oxygen was given (fresh gas flow 3 litre min\(^{-1}\)). When breathing was adequate, the tracheal tube was removed.

**Memory assessment**

When the patients regained consciousness and opened their eyes spontaneously after anaesthesia, they were asked to name precisely an object that they were shown. This was a red booklet, which was opened and closed in front of them. They were asked to keep this booklet in mind.

The next day, the patients were asked about their memory after immediate waking using a structured interview. They were asked to keep in mind.

The present investigation describes memory performance, while recovery of MnSSER with decreasing anaesthetic dose has been published previously.6

**Table 1 Structured interview 24 h after anaesthesia**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
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<tbody>
<tr>
<td>Do you remember whether the MnSSER recording was performed?</td>
<td>Yes</td>
</tr>
<tr>
<td>What was the first you remembered after waking up from anaesthesia?</td>
<td>Name</td>
</tr>
<tr>
<td>Do you remember anything to be shown to you during the wake-up period?</td>
<td>No</td>
</tr>
<tr>
<td>Do you remember whether the MnSSER recording was performed?</td>
<td>No</td>
</tr>
<tr>
<td>Were you asked to keep anything in mind during recovery from anaesthesia?</td>
<td>Yes</td>
</tr>
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</table>

**MnSSER recording**

The day before surgery the patients were accustomed to MnSSER recording to obtain awake baseline values. The MnSSER recording was performed in a standardized way with an Evomatic 4000® system (Dantec, Copenhagen, Denmark). In preference the right median nerve was stimulated, but if the planned operation made that difficult, the median nerve was used. The individual sensory and motor threshold was defined. The stimulus intensity was increased to the individual level of tolerance and kept constant throughout the whole study. Two replicate baseline recordings were performed. The stimulus frequency was 3 Hz, with a monophasic rectangular pulse of 0.2 ms. The MnSSER waveforms were recorded simultaneously on three amplifier channels using sterile platinum needle electrodes placed over the ipsilateral brachial plexus (Erb’s point), the spinous process of the sixth cervical vertebra and the contralateral cortical hand area at the scalp (C3’ or C4’). A frontal reference (Fpz) was used. Electrode impedances were kept below 10 kΩ. For the baseline data a post-stimulus period of 90 ms was analysed, during anaesthesia and recovery a period of 180 ms. For each response, 200 stimuli were averaged and stored on disk for later analysis. The Evomatic device includes an automatic artefact rejection mode, and the evoked responses at Erb’s point and at the spinous process level served as a control for artefacts, analysed by visual inspection. The latencies and the peak-to-peak amplitudes were obtained using a software package (EvoPC®, Müller, Hamburg, Germany). The following peak latencies were obtained: N10 at Erb, N13 at C6 and three negative components (N20, N35, N50) and two positive peaks in between (P25, P45) at the scalp.
Two replicate MnSSER recordings were performed the day before surgery (AWAKE), during anaesthesia after surgery had finished (ANAESTHESIA) and when the patients opened their eyes spontaneously and named the shown object correctly after anaesthesia (RECOVERY).

Clinical measurements
We recorded heart rate (beats min⁻¹), mean arterial pressure (mm Hg), percutaneous oxygen saturation (%), and arm and body temperature, at the time the MnSSER recording was made. During and after anaesthesia the end-tidal carbon dioxide concentration was measured (either from the tracheal tube, or from a face mask, which was applied firmly and the patient was asked to take some deep breaths).

Statistical analysis
The statistical analysis was done using SPSS version 9.0 (Statistical Package for Social Sciences). The patient details of the different groups were compared a posteriori with Scheffe’s test. The mean and the standard deviations (SD) of the various cortical peak latencies and amplitudes were calculated, and the inter-wave conduction times of the latency components were calculated: LatN20 – LatC6 (CCT=central conduction time), LatP25 – LatN20, LatN35 – LatP25, LatP45 – LatN35, and LatN50 – LatP45. The distribution of the data was tested by the Kolmogorov–Smirnov test. The correlation coefficients were separately defined for the five latencies, the five inter-peak latencies, and the four amplitudes.

Inter-group comparisons for the MnSSER latencies (five components), the latency differences (five components), and the amplitudes (four components) for the three memory groups were assessed by multivariate analysis of variance (MANOVA, Hotelling’s T-square) including AWAKE and RECOVERY values. Multivariate comparisons were performed for the five latency components, the five inter-peak latency components and the four cortical amplitudes separately at AWAKE, ANAESTH, and RECOVERY values. For each MnSSER component, univariate analysis of variance compared the data at AWAKE and RECOVERY. The sensitivity and specificity were calculated for the significant MnSSER components to define cuff-off values for memory performance. P<0.05 was adopted for level of significance for all statistical tests.

Results
Explicit and implicit memory
At interview 24 h after anaesthesia, 15 patients had no memory for the immediate wake-up period. Eleven patients had implicit memory for the booklet, and 23 had explicit memory. Of these 23, 13 remembered the booklet spontaneously and 12 recalled at least one MnSSER recording being performed. However, another three patients spontaneously described precisely being asked to take a deep breath from the mask, which was tightly pressed on their face. They were included in the group EXPLICIT, because this procedure was done during the immediate recovery period to measure respiratory values. Only five patients remembered both the MnSSER recording and the booklet spontaneously. However, another four had implicit memory for the shown booklet, and remembered the MnSSER recording. One patient, who recalled taking a deep breath, had implicit memory for the booklet. However, two patients of the group EXPLICIT recalled extubation.

MnSSER components
Satisfactory MnSSER traces were obtained at the different measurements from all patients. Figure 1 gives examples of the MnSSER recordings of three patients, one without any memory, one with implicit memory, and one with explicit memory. There was no difference for any of the MnSSER components at AWAKE among the three memory groups. Multivariate analysis showed an overall significant difference between the three groups, comparing the MnSSER data at AWAKE and RECOVERY for the latency components and for the inter-wave conduction times (Table 2A–C). The cortical amplitudes did not differ significantly. The MnSSER data at ANAESTH were not included in the multivariate test, because N35 was completely suppressed in seven patients, P45 in 16 and N50 in 22 patients, thus reducing n for statistical testing markedly. However, univariate comparison at ANAESTH revealed significantly shorter latencies N20 and P25, comparing patients of group EXPLICIT with patients of group NO-MEM (P<0.05). The components ≥35 ms were completely reduced in more patients of group NO-MEM and IMPLICIT than in patients of group EXPLICIT (Fig. 2).

At RECOVERY Hotellings’ T-square showed significant main effects for the latency (P<0.01) and the inter-wave conduction times (P<0.001) among the three memory groups. The amplitudes did not differ at RECOVERY. ANOVA showed significant differences for latencies P45 (P<0.05) and N50 (P<0.01), as well as for the conduction times LatP45 – LatN35 (P<0.01) and LatN50 – LatP45 (P<0.05). Post hoc comparison revealed significant shorter latencies P45 (P<0.05) and N50 (P<0.05) and inter-peak latency LatN35 – LatP45 (P<0.05) for the patients of the group EXPLICIT compared with the patients of the group NO-MEM. Using a cut-off value of 14 ms for the latency P45 yielded a sensitivity of 87.0% and a specificity of 61.5% to predict patients with no memory (for N50, a cut-off value of 21 ms, sensitivity 69.6%, specificity 76.9%).

The MnSSER data of the three memory groups did not differ in relation to the used anaesthetic. However, the
changes of latencies P45 and N50 and inter-wave conduction times LatN35 – LatP45 and LatP45 – LatN50 were significantly correlated with the duration of anaesthesia ($P=0.016$ for latencies, $P=0.007$ for inter-wave conduction times).

Clinical measurements

There was no difference among the three memory groups in their physical characteristics (Table 3) or the clinical measurements between the three memory groups at AWAKE, ANAESTH, or RECOVERY. The time of extubation and RECOVERY, when the patients opened their eyes spontaneously, did not differ among the groups. In contrast, the time of anaesthesia was significantly less in the patients of the group EXPLICIT (mean 88 (sd 32) min) than in the group IMPLICIT (113 (40) min), and the group NO-MEM (112 (28) min; Table 2).

Additional opioid dose did not differ among the groups. The total amount of opioid for the different memory groups was: fentanyl (mg kg$^{-1}$ h$^{-1}$; in combination with isoflurane): group NO-MEM: 0.019 (0.001) ($n=7$); group IMPLICIT: 0.021 (0.001) ($n=8$); group EXPLICIT: 0.022 (0.001) ($n=14$); $P=0.643$. For sufentanil (mg kg$^{-1}$ h$^{-1}$; in combination with propofol): group NO-MEM: 0.45 (0.15) ($n=8$); group IMPLICIT: 0.35 (0.07) ($n=3$); group EXPLICIT: 0.43 (0.06) ($n=9$); $P=0.387$. In the patients who received isoflurane, the end-tidal isoflurane concentration did not differ between the three groups at RECOVERY.

Discussion

We found that spontaneous recall for recovery was impaired in 53% of patients after general anaesthesia. The information, which was recalled 24 h post-operatively, was not the same for all patients. Some patients remembered a shown object, others the electrical stimulation of the median nerve or the face mask. Twenty-two per cent of the patients had implicit memory function. The mid-latency MnSSER components P45 and N50 and the inter-wave conduction time LatN35 – LatP45 were significantly shorter in the patients who had explicit memory than in the patients, who did not have any memory. However, the MnSSER data did not differ among the patients with or without implicit memory formation.

We wished to assess in a descriptive way the recovery of memory and MnSSER changes in clinical circumstances. We cannot attribute our findings to a single anaesthetic substance or anaesthetic regimen, because the statistical power to evaluate this question is low (three memory groups, two anaesthetic regimens). However, all the patients were pre-medicated with midazolam, a substance to be amnesic.7 A more pronounced effect would have been expected in the patients in whom the total time of anaesthesia was shorter. In contrast, these patients especially, had explicit memory in the present study. Therefore, we concluded that midazolam did not affect our results.

The total time of anaesthesia was significantly shorter in the patients who had recall. Because the infusion rate for propofol and the concentration of isoflurane were fixed, the total quantity of anaesthetic increased with the duration of anaesthesia. Therefore, most probably residual anaesthetic
agents would be different in the patients and affect memory performance. The chosen clinical endpoint of the patients’ responsiveness, that is that all patients were able to recognize and verbally define a shown object, did not allow prediction of the patients’ memory. Dutton and colleagues found no evidence of memory formation in 13 out of 28 patients, as long as the patients did not sustain wakefulness sufficiently long enough to complete four hand squeezes. Unfortunately we did not test this clinical sign.

The latency of the primary cortical complex of the tibial nerve SSER is changed by high doses of fentanyl and sufentanil. In the present study the time of the last dose and amount of opioids given per hour did not differ between the groups. Although the effect sizes of the group differences

<table>
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<th>Error DF</th>
<th>Significance of F</th>
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<tr>
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<tr>
<td>3</td>
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<td>0.000</td>
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Table 2: Statistical results analysis of variance (between and within subject designs) for MnSSER latency components, inter-peak latencies and amplitudes including AWAKE and RECOVERY

![MnSSER amplitudes N50](image)

Fig 2: MnSSER amplitudes N50 of individual subjects with bars indicating the means are shown. Group NO-MEM (n=15) without memory, group IMPLICIT (n=11) with implicit memory and group EXPLICIT (n=23) with explicit memory for the immediate wake-up phase from anaesthesia. White symbols, isoflurane/nitrous oxide; black symbols, propofol/sufentanil. N50 was suppressed completely during anaesthesia in 22 patients.
found in the present study do not suggest any clinical relevance, further studies are needed to exclude the effects of opioids on memory performance and/or MnSSER changes.

Our findings support data from volunteer studies, that memory is impaired by subanesthetic concentrations, when responses to command are still present. Dwyer and colleagues showed in 12 healthy volunteers that conscious memory is impaired by subanesthetic concentrations, when at 0.45 MAC isoflurane, while 0.6 MAC nitrous oxide related to unconscious memory was completely suppressed. Veselis and colleagues found different effects of nitrous oxide on psychophysical tests involving declarative or procedural memory. Alkire and colleagues demonstrated in PET-studies, that anaesthetic effects are not uniformly distributed in different brain areas. In the present study the MnSSER components P45 and N50 differed between the patients with and without explicit memory, whereas the earlier components did not. Different parts of the brain are responsible for the MnSSER components. The parts that form P45 and N50 could be affected in the same way as the neurons which are involved in memory formation, so that impairment of memory formation and changes of MnSSER components occur simultaneously. It is unlikely that MnSSER changes directly reflect memory formation of other sensory systems, like the visual system, which was activated in memory processing for the shown object.

Evidence suggests that EEG measures may suggest the likelihood of memory formation intra-operatively. Liu and colleagues found that the bispectral index, a variable derived from the spontaneous EEG, correlated with intra-operative picture recall during propofol bolus injection. Patients having cardiac surgery, an increase of the AER latency Pa of greater or less than 12 ms distinguished among patients with and without implicit memory post-operatively. Some recognition of an auditory stimulus may be affected in the same way as the neurons which are involved in memory formation, so that impairment of memory formation and changes of MnSSER components occur simultaneously. It is unlikely that MnSSER changes directly reflect memory formation of other sensory systems, like the visual system, which was activated in memory processing for the shown object.
was absent during recovery from general anaesthesia. However, sensitivity and specificity are not sufficient to recommend MnSSER as a measurement for everyday clinical routine. More research is needed to show if MnSSER components indicate memory during surgical anaesthesia.

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