Background. We investigated the relationship between median nerve somatosensory evoked potentials (SSEPs) and the bispectral index (BIS) during alternating periods of consciousness and propofol-induced unconsciousness.

Methods. Loss of consciousness (LOC) was repetitively induced by bolus injections of propofol in 24 patients undergoing elective surgery in spinal anaesthesia. SSEP and the BIS were recorded during LOC and recovery of consciousness (ROC). The level of consciousness was clinically assessed by the observer’s assessment of alertness/sedation scale. Propofol venous plasma concentrations were measured simultaneously.

Results. At LOC, all SSEPs latency components were prolonged ($P<0.001$), whereas amplitudes of the components $\geq 45$ ms were smaller ($P=0.008$) and the BIS values were lower ($P<0.001$). None of the EEG variables regained baseline levels during ROC. Regression analyses revealed that the SSEP components (five latencies and five amplitudes) explained 33% of the variance when predicting ROC; the BIS explained 12%. The combination of SSEP and BIS explained 37% of variance in this patient sample. Propofol venous plasma concentration was $1.2 (0.8) \mu g$ $ml^{-1}$ during LOC and $0.4 (0.5) \mu g$ $ml^{-1}$ during ROC.

Conclusions. The present results indicate the usefulness of combining variables of the evoked and spontaneous EEG to measure different levels of consciousness, because the SSEP provide additional information beyond the BIS. Inter-individual variability of all the EEG variables limits their predictive potency of ROC after propofol infusion.

Keywords: anaesthesia, depth; anaesthetics i.v., propofol; brain, electroencephalography

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SSEP and propofol induced different states of consciousness

that these variables measure different aspects of neural processing during anaesthesia. Vereecke and colleagues recently published data about a new composite AAI1.6 index, which combines information of the AEP and the spontaneous EEG. The authors found that the new index showed a better correlation to the calculated effect-site concentration of propofol than the commercially available AAI1.5 index, which extracts information of the AEP only.

In previous studies, we could show that somatosensory evoked potentials (SSEPs) are a useful tool to quantify electrical activity of the brain during and after surgery. For the present investigation, we used a study design introduced by Davies and colleagues and later reproduced by other authors. Davies and colleagues could demonstrate that AEP showed consistent changes during repeated transition from consciousness to unconsciousness induced by propofol, when nociceptive input was blocked by spinal anaesthesia. The aim of the present study was to investigate SSEP, the bispectral index (BIS), and propofol plasma concentration in relation to a clinical sedation score during propofol-induced periods of unconsciousness. The level of consciousness was assessed by Avramov’s sedation score; thus, the loss of consciousness (LOC) was defined as being unresponsive to verbal command and mild shaking or prodding. The hypothesis was that (i) midlatency SSEP components correlate with the clinical assessment, thus differentiating between being conscious or unconscious and (ii) SSEP and BIS together give more detailed information about the level of consciousness than a single EEG variable.

Methods

After obtaining approval from the local ethics committee and written informed consent, 24 patients, undergoing elective urologic surgery or surgery of the lower extremities with spinal anaesthesia, were included in this prospective study. Patients with neurological or psychiatric diseases were excluded. Known adverse effects to the used medications, pregnancy, and age >70 yr were also exclusion criteria. The patients did not take any centrally acting drugs.

Anaesthesia

All patients received midazolam 0.1 mg kg⁻¹ orally as a premedication 45 min before anaesthesia. After arrival at the operation theatre, all patients’ vital signs were monitored with 5-lead ECG, non-invasive arterial pressure, and pulse oximetry. An 18 G cannula was inserted into the forearm vein. Fluid preload was given with 500 ml crystalloids. Pulseoxymetric oxygen saturation and heart rate were recorded continuously; non-invasive mean arterial pressure was documented every 5 min. The patients were placed on a heating blanket and covered with blankets during the whole procedure in order to avoid a decrease in temperature.

Spinal anaesthesia was performed with a lumbar puncture using a 26 G pencil point needle either at L3/L4 or at L4/L5. In relation to body height, 15–18 mg isobaric bupivacaine (0.5%) was injected intrathecally. Surgery was allowed to start after spinal anaesthesia had spread to the level of TH10 bilaterally. All patients received oxygen 2 litre min⁻¹ during the procedure.

After EEG baseline recordings had been obtained, 20 mg propofol were repetitively injected every 30 s till the patient lost consciousness. Hereby, LOC was defined as no response to verbal command and mild shaking or prodding. After LOC, a propofol infusion 2 mg kg⁻¹ h⁻¹ was started till one measurement of evoked potentials was finished. Then, the propofol infusion was stopped. Another EEG measurement was performed, when consciousness returned. Hereby, ROC was defined as being able to press the hand four times on command. The whole procedure was practiced three times (Fig. 1).

Median nerve SSEPs were elicited by electrical stimulation at the wrist (Keypoint®, Medtronic, USA). After defining the individual sensory and motor threshold, the stimulation intensity was adapted to the individual threshold of tolerance. At the scalp, skin resistance was reduced by preparation of the skin with Softasept (Braun Melsungen AG, Melsungen, Germany) and skin preparation gel Skin Pure (Nihon Kohden Corporation, Tokyo, Japan). Evoked potentials were recorded at C3 vs Fz according to the International 10–20 System, furthermore at Erb and C2, in order to control correct stimulus delivery. Bandpass was set 20–2000 Hz; stimulation frequency was 3 Hz. Two hundred sweeps were averaged per measurement. Cerebral drug effect was assessed using the BIS, using the Aspect A 2000 Monitor (Aspect Medical System Norwood, MA, USA, Version 2.21) with BIS Quatro™ electrodes placed on the frontal skin (Aspect Medical Systems). The frontal skin was prepared with Softasept® N (B. Braun Melsungen AG) to achieve electrode impedances below 5 kΩ.

Clinical assessment of the level of consciousness was done using the observer’s assessment of alertness/sedation scale according to Avramov. Hereby, level 1 indicated a fully alert patient and level 5 unresponsiveness (Table 1).

Propofol plasma concentration was measured in parallel to the EEG data acquisition. A blank blood probe was taken immediately after the first venous cannula was inserted. A second cannula was placed into the other forearm, when the patients lost consciousness for the first time. Blood samples for propofol analysis were withdrawn into EDTA tubes and refrigerated until centrifugation within a few hours. Plasma was then transferred into storage tubes with no extra contents and frozen at –40°C until analysis. The propofol concentration in plasma was determined by high performance liquid chromatography with photodiode array detector (HPLC-DAD). Two hundred microlitres acetonitrile were added to 200 µl serum for protein precipitation. After 5 min vortexing and
centrifugation, 50 μl of the supernatant were injected for HPLC. The detection wavelength was 219 nm with a bandwidth of 10 nm. The method was calibrated and validated according to the guidelines of the Society of Toxicological and Forensic Chemistry. The limits of detection and of quantification were 0.05 and 0.15 μg ml⁻¹, respectively. Details about the used instruments and HPLC conditions were described elsewhere.¹⁹

**Statistics**

The amplitudes and the latencies of the five midlatency SSEP components (N20, P25, N35, P45, and N55) were calculated. Statistical analyses were performed using SPSS version 15. The SSEP data were analysed using multivariate analysis of variance (MANOVA) (Hotellings T²-square; repeated measurement design) after testing the required normal distribution using Kolmogorov–Smirnov test with the Lilliefors correction.²⁰ All seven time points were included in the overall multivariate analysis resulting in a full two-factor-within design (dependent variables: latency/amplitude measure; time). Simultaneously collected BIS data were included in the analysis.

Using the level of consciousness (Avramov’s index) as dependent variable in a multiple regression, BIS and SSEP components (five latencies and five amplitudes) were separately tested as predictor variables. In order to analyse whether variables of the spontaneous and the evoked EEG in combination improve the prediction of recovery from the unconscious state stepwise regression analysis was utilized. Explained variance $R^2$ is reported.

General linear modelling (GLM) was used to analyse the trend components of the dose of propofol administered to induce LOC during three time points (LOC 1–3). On an explanatory basis, propofol plasma concentrations were compared over six time points. $P \leq 0.05$ was adopted as level of significance for all tests. Results are given as means (sd), unless stated otherwise.

**Results**

Sufficient EEG recordings were obtained in 22 out of 24 patients. Two patients were excluded from the study, because the EEG tracks were corrupted by muscle artifacts, when baseline measurements were recorded. From the remaining 22 patients, sufficient recordings were obtained at baseline and during the LOC2/ROC2 period. In one patient, it was not possible to identify the SSEP

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**Fig 1** The study design is depicted. BIS, bispectral index; SSEP, median nerve somatosensory evoked potential; BL, awake; LOC, loss of consciousness induced by propofol; ROC, recovery of consciousness.

**Table 1** Avramov’s scale to assess the level of consciousness

<table>
<thead>
<tr>
<th>Score</th>
<th>Responsiveness</th>
<th>Speech</th>
<th>Facial expression</th>
<th>Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Responds readily to name spoken in normal tone</td>
<td>Normal</td>
<td>Normal</td>
<td>Clear, no ptosis</td>
</tr>
<tr>
<td>2</td>
<td>Lethargic, responds to name spoken in normal tone</td>
<td>Mild slowing or thickening</td>
<td>Mild relaxation</td>
<td>Glazed or mild ptosis (less than half the eyes)</td>
</tr>
<tr>
<td>3</td>
<td>Responds only after name is called loudly, repeatedly, or both</td>
<td>Slurring or prominent slowing</td>
<td>Marked relaxation (slack jaw)</td>
<td>Glazed or mild ptosis (less than half the eyes or more)</td>
</tr>
<tr>
<td>4</td>
<td>Responds only after mild prodding or shaking</td>
<td>Few recognizable words</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Does not respond to mild prodding or shaking</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Rundshagen et al.
SSEP and propofol induced different states of consciousness

Peaks during LOC1/ROC1 because EEG signals were corrupted by electrical interference; in another patient, no recordings were performed during LOC3/ROC3, because the study had to be stopped, when the surgery was completed. Overall, incomplete data were obtained from nine patients and hence excluded from repeated measurement analysis. No significant differences were found between patients with complete and incomplete data with respect to any SSEP component or the BIS at any time, supporting the assumption of missing at random. Patient characteristic data of the 22 remaining patients were as follows: age, 62 (range 30–70) yr; weight, 79 (54–115) kg; height, 176 (157–191) cm; five females, 17 males; and ASA classification I (7), II (13), and III (2).

Propofol-induced changes of SSEP and BIS: SSEP baseline recordings, when the patients were awake, did not differ substantially from reference data in the literature. Table 2 and Figure 2 summarize the results for the SSEP components and the BIS. MANOVA revealed significant changes of the SSEP midlatency components during repetitive administration of propofol, when the patients lost consciousness (Table 3). All latency components were prolonged during LOC measurements. The prolongation was more pronounced for the later SSEP latencies as a significant interaction between SSEP latencies and time indicated (P<0.001). SSEP amplitudes were less affected; the significant interaction between SSEP amplitudes and time indicated the later SSEP amplitudes >45 ms were markedly reduced by propofol at LOC, too (P<0.001). N55 was completely suppressed in five patients during LOC; P45 in two patients. BIS was significantly lower, when the patients lost consciousness. BIS and SSEP latency components did not regain baseline level during ROC periods and remained substantially prolonged or, in the case of the BIS, lower (P<0.001 vs BL, post hoc analyses with dependent T-test).

SSEP and BIS were analysed as predictors for recovery of consciousness (ROC). When Avramov’s score was used as a dependent variable during the periods of ROC, BIS explained 12% of variance (R²=0.12). SSEP components (five latencies and five amplitudes) explained 33% of variance (R²=0.33). As seen in Table 4, latency components were more powerful predictors than amplitudes. Adding BIS in a stepwise regression analysis to the SSEP components as predictors of Avramov’s score during recovery increased the R² by 4% to 0.37. Redundancy analysis showed that the squared multiple correlation of SSEP variables with BIS was 29%.

The results of the clinical assessment of sedation are shown in Figure 3. Avramov’s score did not return to baseline levels during ROC periods.

The mean venous plasma concentration of propofol was 1.2 (0.8) µg ml⁻¹ during LOC and 0.4 (0.5) µg ml⁻¹ during ROC. Figure 4 depicts the measured plasma concentrations at different time points. MANOVA indicated significant differences over time during all LOC and ROC periods (F=17.72; P=0.02). GLM indicated a significant linear trend over time during recovery, resulting in lower plasma concentrations at ROC2 and ROC3 compared with ROC1 (P=0.029). The bolus doses of propofol needed to induce LOC were significantly higher at LOC1 [61 (19) mg] than at LOC2 [44 (15) mg] and LOC3 [43 (17) mg] as indicated by a significant linear and quadratic trend component (P≤0.006). The doses of propofol inducing unresponsiveness showed a significant negative correlation to the age of the patients (at LOC1: r=-0.8, at LOC2: r=-0.5, at LOC3: r=-0.5, P≤0.03).

Although MAD and pulseoxymetric oxygen saturation remained constant over time, the heart rate was decreasing slightly over time from 67 (13) beats min⁻¹ at BL to 60 (10) beats min⁻¹ at ROC3.

### Discussion

The described alterations of the SSEP and the BIS indicate the gradual hypnotic effect of propofol on the brain, resulting in different levels of consciousness, as assessed by Avramov’s scale. Our design was related to standard clinical practice in our hospital. Therefore, the described

<table>
<thead>
<tr>
<th>Time</th>
<th>BL</th>
<th>LOC1</th>
<th>ROC1</th>
<th>LOC2</th>
<th>ROC2</th>
<th>LOC3</th>
<th>ROC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latencies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L N20</td>
<td>21.5 (1.3)</td>
<td>22.1 (1.6)</td>
<td>22.0 (1.4)</td>
<td>23.0 (2.0)</td>
<td>22.4 (1.5)</td>
<td>23.2 (1.8)</td>
<td>22.5 (1.7)</td>
</tr>
<tr>
<td>L N25</td>
<td>25.0 (2.0)</td>
<td>28.7 (2.3)</td>
<td>27.9 (2.1)</td>
<td>29.9 (2.9)</td>
<td>28.4 (2.1)</td>
<td>30.7 (3.0)</td>
<td>28.7 (1.9)</td>
</tr>
<tr>
<td>L N35</td>
<td>36.8 (4.5)</td>
<td>43.1 (6.0)</td>
<td>38.7 (3.6)</td>
<td>45.3 (5.8)</td>
<td>40.5 (4.1)</td>
<td>47.3 (7.1)</td>
<td>41.2 (3.9)</td>
</tr>
<tr>
<td>L N45</td>
<td>47.5 (7.0)</td>
<td>69.6 (10.9)</td>
<td>56.7 (6.4)</td>
<td>75.0 (15.4)</td>
<td>60.1 (6.7)</td>
<td>74.4 (12.3)</td>
<td>59.5 (7.5)</td>
</tr>
<tr>
<td>L N55</td>
<td>66.3 (11.1)</td>
<td>100.8 (22.1)</td>
<td>77.1 (9.9)</td>
<td>103.8 (21.3)</td>
<td>81.7 (6.5)</td>
<td>104.2 (17.6)</td>
<td>81.5 (7.6)</td>
</tr>
<tr>
<td>Amplitudes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A N20</td>
<td>2.1 (1.2)</td>
<td>1.7 (1.1)</td>
<td>2.0 (1.3)</td>
<td>2.1 (1.5)</td>
<td>1.8 (1.4)</td>
<td>2.1 (1.6)</td>
<td>1.9 (1.3)</td>
</tr>
<tr>
<td>A N25</td>
<td>2.4 (3.0)</td>
<td>2.1 (2.2)</td>
<td>1.9 (1.5)</td>
<td>2.0 (1.7)</td>
<td>2.3 (1.8)</td>
<td>1.9 (1.6)</td>
<td>2.2 (2.0)</td>
</tr>
<tr>
<td>A N35</td>
<td>1.2 (1.2)</td>
<td>2.1 (1.3)</td>
<td>1.8 (0.7)</td>
<td>1.9 (1.3)</td>
<td>1.8 (1.2)</td>
<td>1.6 (1.3)</td>
<td>1.8 (1.0)</td>
</tr>
<tr>
<td>A N45</td>
<td>2.9 (1.7)</td>
<td>1.35 (0.9)</td>
<td>2.1 (1.6)</td>
<td>1.2 (0.9)</td>
<td>1.9 (1.6)</td>
<td>1.4 (1.1)</td>
<td>1.5 (1.3)</td>
</tr>
<tr>
<td>A N55</td>
<td>1.9 (1.5)</td>
<td>1.08 (0.9)</td>
<td>1.9 (2.1)</td>
<td>0.7 (0.8)</td>
<td>1.7 (1.6)</td>
<td>0.9 (1.1)</td>
<td>1.8 (1.5)</td>
</tr>
<tr>
<td>BIS</td>
<td>92 (8)</td>
<td>66 (8)</td>
<td>81 (5)</td>
<td>65 (11)</td>
<td>79 (5)</td>
<td>64 (11)</td>
<td>81 (6)</td>
</tr>
</tbody>
</table>
Fig 2 Individual SSEP latency components and BIS are shown. BL, awake; LOC, loss of consciousness induced by propofol; ROC, recovery of consciousness. n=22 (patients with incomplete data set are included in this figure).

Table 3 Statistical results of the analysis of variance (between- and within-subject design) for SSEP latency and amplitude components and the BIS including LOC and ROC periods. Hyp, hypothetic; DF, degree of freedom; Sign, significance

<table>
<thead>
<tr>
<th></th>
<th>Exact F</th>
<th>Hyp F</th>
<th>DF</th>
<th>Sign of F</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSEP latencies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>314.64</td>
<td>6</td>
<td>6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Latency</td>
<td>32.29</td>
<td>4</td>
<td>8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interaction</td>
<td>19.46</td>
<td>24</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SSEP amplitudes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>6.41</td>
<td>6</td>
<td>6</td>
<td>0.020</td>
</tr>
<tr>
<td>Amplitude</td>
<td>7.45</td>
<td>4</td>
<td>8</td>
<td>0.008</td>
</tr>
<tr>
<td>Interaction</td>
<td>17.85</td>
<td>24</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>19.39</td>
<td>6</td>
<td>9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4 Results of the multiple regression analyses: the level of consciousness (quantified by Avramov’s index) is utilized as dependent variable; the SSEP amplitude and latency components are tested as predictor variables

<table>
<thead>
<tr>
<th>Model</th>
<th>Standardized coefficients</th>
<th>t</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>N20</td>
<td>-0.41</td>
<td>-2.23</td>
<td>0.030</td>
</tr>
<tr>
<td>P25</td>
<td>0.60</td>
<td>3.09</td>
<td>0.003</td>
</tr>
<tr>
<td>N35</td>
<td>-0.31</td>
<td>1.35</td>
<td>0.184</td>
</tr>
<tr>
<td>P45</td>
<td>0.49</td>
<td>1.91</td>
<td>0.062</td>
</tr>
<tr>
<td>N55</td>
<td>0.02</td>
<td>0.08</td>
<td>0.935</td>
</tr>
<tr>
<td>Amplitude</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N20</td>
<td>-0.28</td>
<td>1.75</td>
<td>0.087</td>
</tr>
<tr>
<td>P25</td>
<td>-0.16</td>
<td>-0.77</td>
<td>0.448</td>
</tr>
<tr>
<td>N35</td>
<td>0.12</td>
<td>0.67</td>
<td>0.506</td>
</tr>
<tr>
<td>P45</td>
<td>0.13</td>
<td>0.62</td>
<td>0.541</td>
</tr>
<tr>
<td>N55</td>
<td>0.21</td>
<td>0.93</td>
<td>0.358</td>
</tr>
</tbody>
</table>
electrical brain activity. This corresponds to the various
variables indicate to some extent different aspects of the
information between the variables was 29%, that is, both
of consciousness. Regression analysis showed that the shared
of a single EEG variable in order to predict the patient’s level
the spontaneous and the evoked EEG is superior to the use
values. We could demonstrate further that the combination of
and Nb were slightly shorter than the consecutive ROC
colleagues,8 who showed that AEP baseline latencies Na, Pa,
accordance with the initial experiment of Davies and
was defined as the clinical endpoint. Our findings are in
the patients were able to squeeze the hand four times, which
an impairment of the brain function was documented, when
SSEP nor the BIS values regained baseline levels. Thus, still
not altered by surgical stimulation, as noxious input was
EEG signals. However, changes in SSEP and BIS were
have slightly modified the level of consciousness and the

SSEP and propofol induced different states of consciousness

effects on EEG variables and changes in consciousness
are not related to steady-state drug concentrations.
Premedication with midazolam and spinal anaesthesia may
have slightly modified the level of consciousness and the
EEG signals. However, changes in SSEP and BIS were
not altered by surgical stimulation, as noxious input was
blocked by spinal anaesthesia.

When the patients became responsive again, neither the
SSEP nor the BIS values regained baseline levels. Thus, still
an impairment of the brain function was documented, when
the patients were able to squeeze the hand four times, which
was defined as the clinical endpoint. Our findings are in
accordance with the initial experiment of Davies and colleagues,8 who showed that AEP baseline latencies Na, Pa,
and Nb were slightly shorter than the consecutive ROC
values. We could demonstrate further that the combination of
the spontaneous and the evoked EEG is superior to the use
of a single EEG variable in order to predict the patient’s level
of consciousness. Regression analysis showed that the shared
information between the variables was 29%, that is, both
variables indicate to some extent different aspects of the
electrical brain activity. This corresponds to the various
anatomical brain structures, where the EEG signals are
recorded from. Different generators of the midlatency SSEP
components are known (primary, secondary somatosensory
cortex, and associated brain areas); the BIS signal is recorded
at the frontal brain area.22 23 Schwinden and colleagues11
recently published data from a patient sample in whom 81
variables (31 EEG, 22 SSEPs, and 28 AEP variables) were
recorded during stable anaesthetic state. The performed
factor analyses indicated that 80% of their observed variance
was explained by 13 factors. None of the derived factors
combined information from the EEG, AEP, and SSEP. The
authors concluded that each of the three electrophysiological
measurements represented different aspects of electrical brain
activity. In a subsequent study, it was shown that combining
EEG variables with AEP and SSEP variables increased the
discriminant power at different clinical states during general
anaesthesia.12 SSEP had the lowest discriminant power,
which the authors attributed to the fact that surgical stimu-
lolation was absent during their measurements. In the present
study, we demonstrated that SSEPs are a useful tool to
discriminate different levels of consciousness in the absence
of noxious input and are additive with the BIS.

Dutton and colleagues17 showed that a patient’s response of
four hand squeezes was associated with memory formation in about 50% of the cases. In contrast, a brief
wakeful response like opening the eyes or one hand
squeeze on command was not associated with memory performance. In the present study, the propofol plasma concen-
tration during ROC periods was similar to concentrations
which have been reported to suppress learning in volun-
teers.24 Moreover, the prolongation of the SSEP latencies
>35 ms reported in the present study was similar to those,
which we found in the absence of explicit memory in
patients after general anaesthesia.15 However, a direct com-
parison of both studies is limited due to the fact that the
study population of the previous investigation was younger
and female only. This time we used a modified structured
interview of Brice and colleagues25 to assess memory in
our patients. We failed to assess memory during LOC
and ROC periods, because the few patients, who reported about
remembering the electrical stimulation at the wrist (that
was all they reported about), were not sure, when that had
happened exactly. Further studies combining SSEP with
distinct memory tests are needed to clarify, whether SSEP
in combination with other EEG variables are suitable to
detect awareness with explicit memory during surgery.

The mean propofol dose at LOC was 50 (19) mg in
the present study. The corresponding venous plasma
concentration was 1.2 (0.8) µg ml⁻¹. Iselin-Chaves and
colleagues26 induced unconsciousness in volunteers by
increasing target effect-site concentration from 1 to 6 µg
ml⁻¹ stepwise. Arterial plasma concentrations were
sampled. The authors calculated a mean propofol plasma
concentration of 4.2 µg ml⁻¹ to induce LOC in 95% of
the volunteers. Mi and colleagues27 measured even higher
plasma concentrations. The authors documented about

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**Fig 3** Means (SD) of clinically assessed level of consciousness (1, awake; 5, not arousable). BL, awake; LOC, loss of consciousness induced by propofol; ROC, recovery of consciousness. *n* = 22.

**Fig 4** Means (SD) of propofol plasma concentration. BL, awake; LOC, loss of consciousness induced by propofol; ROC, recovery of consciousness. *n* = 22.
6–23 μg ml⁻¹ propofol in arterial blood samples, when LOC was induced by injecting 30 mg kg⁻¹ h⁻¹. To some extent, these discrepancies are due to the study populations and the different sample sites for the blood probes. Moreover, the discrepancies are related to the induction speed of propofol. Owing to hysteresis, a high arterial plasma concentration corresponds to a sufficient effect-site concentration in the brain to induce LOC.

In the present study, the SSEPs and the BIS showed a large inter-individual range in relation to the clinical assessment. This is in line with other studies evaluating EEG variables. In general, this limits the predictive potency of an EEG variable in the individual case and the determination of thresholds. However, most probably, the clinical assessment of distinct changes of consciousness is not exact, too. This might cause a study bias in general. Consciousness is a complex phenomenon and its definition and quantification remains complex, too.

Offline analysis unfortunately limits the broader application of SSEPs to quantify the pharmacodynamics of anaesthetics during clinical routine till now. Our method is based on analysing the latencies and amplitudes of the five midlatency SSEP components. Schwilden and colleagues used wavelet analyses to decompose the SSEP signals and to extract 21 variables. Huotari and colleagues introduced graphoelements as bursts, spindles, and sharp waves after median nerve stimulation to demonstrate the effects of deepening propofol anaesthesia.

To summarize, the present study shows the applicability and the limitations of SSEP to quantify changes in consciousness, when the patients receive propofol during spinal anaesthesia. The combination with the BIS gives more detailed information about the level of consciousness than each of the EEG variables alone.

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