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Identification of Sensory Blockade by Somatosensory and Pain-induced Evoked Potentials

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Background: **To date, the anesthesia-induced blockade of nociceptive inputs is insufficiently reflected by commercially available electroencephalographic depth-of-anesthesia monitors. The aim of the current study was to evaluate the potential of somatosensory (SSEP) and intracutaneous pain evoked (iSEP) potentials during remifentanil and propofol anesthesia as electroencephalographic indicators of the nociceptive blockade.**

Methods: **Ten healthy men were investigated in a double-blind crossover design during three sessions with remifentanil, propofol, and placebo administration. All dosages were increased in a step-by-step mode. SSEP and iSEP recordings were performed followed by subjective pain ratings and measurement of level of sedation (modified Observer's Assessment of Alertness and Sedation Scale). Changes from baseline in evoked potential components, pain ratings, and sedation scale were assessed by Bonferroni-Holms–corrected Wilcoxon tests.**

Results: **Pain ratings were significantly reduced by remifentanil. Sedation scale was significantly reduced by propofol. Early SSEP components were not affected by medication. The amplitudes of the long latency SSEP components increased significantly with remifentanil, decreased with propofol, and did not change with placebo. The amplitudes of long latency components of the iSEP decreased significantly with both remifentanil and propofol and did not change with placebo.**

Conclusion: **Long latency components of the SSEP are differently affected by remifentanil and propofol administration. Further studies are needed to clarify whether they can serve as a specific indicator of the nociceptive blockade during anesthesia.**

THE anesthetic state encompasses drug-induced sedation or hypnosis, analgesia, amnesia, lack of movement in response to surgical incision, and prevention of autonomic responses. These components are arranged in a descending hierarchy to correspond with a concept of deepening anesthesia.[1] Two important components are the absence of consciousness (sedation or hypnosis) and the absence of nociception (analgesia). Modern commercial electroencephalographic-based monitoring systems, such as the Bispectral Index (Aspect Medical Systems; Newton, MA),[2] Narcotrend (MonitorTechnik, Bad Bramstedt, Germany),[3] Datex Ohmeda M-Entropy Module (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland),[4] SNAP (Everest, Chesterfield, MO),[5] Cerebral State Monitor (Danmeter, Odense, Denmark),[6] Patient State Analyzer[7] (Hospira, Lake Forest, IL), and AEP Monitor/2 (Danmeter),[8] apply different algorithms to the electroencephalogram to estimate the depth of sedation. However, none of these indices are able to specifically reflect the analgesic component of general anesthesia.[8–12]

Because overdosage as well as underdosage of opioids (*e.g.*, remifentanil) may increase postoperative pain,[13] the development of a depth-of-analgesia monitor to add to the available depth-of-sedation monitors is desirable and necessary. In recent years, evoked potentials using median nerve (SSEP) and intracutaneous stimulation (iSEP) have been introduced to estimate pain.[14,15] Especially the pontine–thalamic components (15–20 ms after the stimulus) of the SSEP were used to measure the analgesic component of balanced anesthesia.[14] Median nerve stimulation activates different nerve types, such as motor (Aα) and mixed sensory (Aβ) nerves. In contrast, the activation of Aδ- and C-fiber as a part of the nociceptive system is in the focus of pain research. For this reason, Bromm *et al.* have established the intracutaneous pain model.[16,17] This model involves removing a small core of epidermis from the skin on the pulp of the finger and placing an electrode directly in the vicinity of Aδ- and C-fiber terminals. Corresponding stimulation evokes clear pinprick pain and brain potentials (iSEP) reflecting the pain sensation. Kochs *et al.*[18] demonstrated that changes in pain perception after different doses of ketamine can be monitored by the iSEP.

The aim of the current study was to evaluate SSEP and iSEP during increasing analgesia with remifentanil and during increasing sedation with propofol. We aimed at identifying an electrophysiologic parameter that could differentiate between remifentanil and propofol.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Materials and Methods

After institutional approval (Ethik-Kommission, Ärztekammer Hamburg, Germany) and written informed consent had been obtained, 10 healthy male adult vol-

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unteers (age range, 22–34 yr; weight range, 69–100 kg) participated in the study. All subjects were free of neurologic disorders and had no history of centrally acting drug intake.

Remifentanil, propofol, and placebo were applied in a random double-blind crossover design on three different days with an intersession interval of 1 week. To realize the double-blind setting, we used a covert intravenous catheter, a black intravenous line, and a syringe pump that was placed outside the investigation room. One subject canceled participation after the first session (remifentanil). For this reason, data from 10 subjects are included in the remifentanil data set and data from 9 subjects are included in the propofol and placebo data sets.

Experimental Session

Each session included nine experimental periods (habituation, baseline, and seven treatment periods). The habituation period was included to familiarize the volunteers with the experimental setup and was excluded from evaluation. After baseline recordings, remifentanil (0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and propofol (target-controlled infusions of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 5.0 μg/ml) were administered in a step-by-step mode (Graseby 3500; Graseby Medical Limited, Watford, Hertfordshire, United Kingdom). Placebo (0.9% NaCl) infusion rate was similar to remifentanil (0.05 mg/ml remifentanil). Up to the time of the study, there was only a commercial target-controlled infusion system for propofol available. For propofol, the target-controlled infusion rate was calculated with the Diprifusor system (Graseby 3500).[19] In case of loss of response to painful trapezius squeeze, the experimental session was stopped before the end of all seven treatment periods.

Experimental Periods

The experimental measurement periods started after reaching the next dosage of the respective investigated drug. Ten minutes after induction of the next higher dosage, SSEP and iSEP recordings were performed, followed by the pain rating and the estimation of the sedation level. The 10-min interval was used to obtain nearly steady state conditions. The following variables were recorded for every period: early and late components of SSEP, early and late components of iSEP, subjective pain ratings, and sedation scale.

SSEP and iSEP

Brain electrical activity was recorded from 128 channels using Ag–AgCl electrodes placed in an equidistant cap layout and referenced to the nose tip (FMS Falk Minow Services, Herrsching, Germany). Electrode impedances were kept below 10 kΩ before the start of the recordings. Electroencephalographic data were recorded using a BrainAmp amplifier system (Brain Products, Munich, Germany) at 16-bit analog–digital conversion (2,500-Hz sampling rate). Signals were band-pass filtered on-line from 0.2 to 1,250 Hz. Epochs contaminated by electrooculographic, myogenic, or other artifacts were eliminated before further analysis using semiautomatic procedures.

The median nerve was stimulated at the wrist with electrical stimuli 7 mA above the motor threshold. Stimuli were presented at a rate of 1 Hz. Evoked responses were averaged over 180 stimuli (3 min). Averaging was performed separately for all subjects and all experimental periods, and results are displayed as a grand mean average, by averaging across subjects. Segments of brain electrical activity containing the SSEP were extracted from the continuous electroencephalographic recordings with segment boundaries from 10 ms before to 40 ms after stimulation (early components: N20 and P25) and from 100 ms before to 200 ms after stimulation (late components: P50 and N150), respectively. For early SSEP components, band-pass filtering was applied from 5 to 1,250 Hz. For the late components, filtering was applied from 0.5 to 150 Hz, and signals were down-sampled to 300 Hz.

Electrical pain stimuli were applied to the tip of the middle finger of the left hand by an intracutaneous technique[16,17,20] with a rate of 1 per 6 s for a period of 4 min (40 stimuli). To induce an unequivocal pain sensation, the epidermal layers of the glabrous skin were carefully removed using a small stainless steel drill (diameter: 1.5 mm), and a metal electrode was inserted and fixed. By application of short constant current impulses (20-ms duration), this procedure activates the most superficial nerve terminals that mostly belong to the nociceptive nervous system (A- and C-fibers).[16,17] The elicited sensation is typically described as pain similar to that evoked by electrical tooth pulp stimulation. Individual pain thresholds were determined at the beginning of each experimental session by a standardized training protocol. Stimuli were applied at twice the intensity of the individual pain threshold. Averaging was performed across 40 epochs for each subject and experimental condition. iSEPs were extracted from the continuous electroencephalographic recordings with segment boundaries from 10 ms before to 40 ms (early components) and from 100 ms before to 900 ms (late components: N150 and P260) after each stimulus onset. For early iSEP components, band-pass filtering was applied from 5 to 1,250 Hz. For the late components, filtering was applied from 0.5 to 150 Hz, and signals were down-sampled to 300 Hz.

A peak extraction of N20, P25, P50, and N150 (SSEP) and N150 and P260 (iSEP) was performed semiautomatically using BrainVision Analyzer software (Brain Products) for all 128 electrodes positions. The spatial topography of SSEP and iSEP components was mapped using triangulation and linear interpolation. For each component and subject, the electrode with the maximum peak amplitude during the baseline period was determined. For further analysis, peak amplitudes were pooled across regions of interest of those

Table 1. Responsiveness Scores of the Modified Observer's Assessment of Alertness and Sedation Scale[20]

Score	Responsiveness
5	Responds readily to demand in normal tone
4	Lethargic response to demand in normal tone
3	Responds only after loud and/or repeated demand
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

six electrodes nearest to the electrode with the maximum peak in the baseline period.

Pain Rating

Pain ratings were used to monitor analgesia. After application of all 40 intracutaneous stimuli, subjects were asked to verbally rate the painfulness of the applied stimuli on a pain rating scale ranging from 0 (no sensation) to 100 (unbearable pain). A scale value of 40 was assigned to the beginning sensation of pain (individual pain threshold). Before each recording session, the pain ratings were trained with the subjects.

Sedation Scale

The subject's responsiveness during pain rating was assessed with the modified Observer's Assessment of Alertness and Sedation Scale (MOAAS; table 1).[20]

Statistical Analysis

For all experimental measurement periods, the significance of changes in the observed variables from baseline were assessed by Bonferroni-Holms[21]–corrected Wilcoxon tests. Correlation between changes in pain ratings, MOAAS, and SSEP and iSEP were quantified by computing Spearman rank correlation coefficients over data pooled across all subjects. P values less than 0.05 were considered to be significant. All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL).

Results

Sensory Blockade

Pain ratings were significantly reduced by remifentanil (59 ± 9 [SD] to 7 ± 14; $P < 0.05$) and propofol (59 ± 7 to 52 ± 11; $P < 0.05$). Remifentanil reduced the pain ratings well below the pain threshold of 40, whereas in the propofol group, the pain ratings remained above the pain threshold. In the placebo group, the pain ratings were unchanged (fig. 1A).

Mental Blockade

The MOAAS was significantly decreased only by propofol (fig. 1B). Seven volunteers reached the deepest sedation level, showing no response to painful trapezius squeeze (MOAAS = 0). In five volunteers, the experimental session was stopped after application of propofol before reaching the highest propofol dosage, *i.e.*, before reaching the last one of all seven treatment blocks.

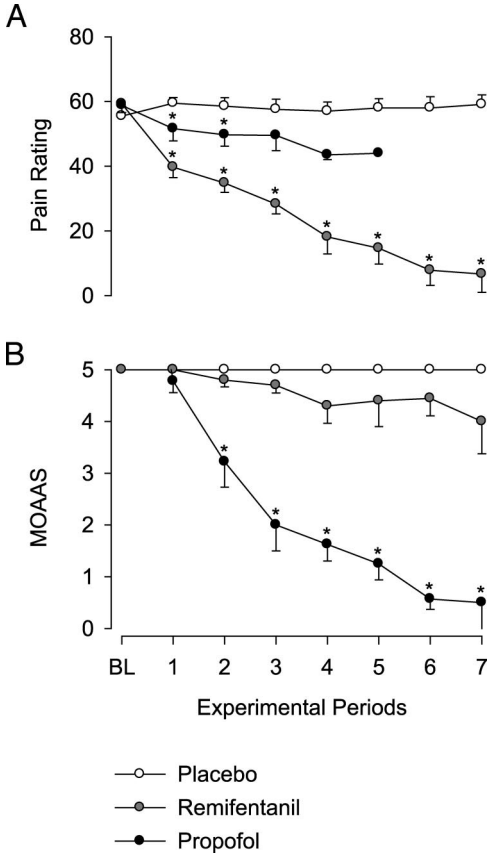

Fig. 1. Pain ratings (*A*) and modified Observer's Assessment of Alertness and Sedation Scale (*B*; MOAAS). Mean and SE before (baseline [BL]) and during stepwise increase (experimental periods 1–7) of placebo (*white circles*), remifentanil (*gray circles*), and propofol (*black circles*). Propofol application resulted in increasing number of volunteers who were not able to verbally rate the painfulness of the applied stimuli (BL [n = 9], experimental period 1 [n = 8], 2 [n = 7], 3 [n = 4], 4 [n = 2], 5 [n = 1], 6 [n = 0], and 7 [n = 0]). In five volunteers, the experimental session was stopped before the end of all seven treatment periods (BL [n = 9], experimental period 1 [n = 9], 2 [n = 9], 3 [n = 9], 4 [n = 8], 5 [n = 8], 6 [n = 7], and 7 [n = 2]). * Statistically significant changes relative to baseline ($P < 0.05$).

Early Components of SSEP

In all participants, artifact-free SSEP components N20 and P25 could be obtained. No changes of early components of SSEP could be obtained after remifentanil, propofol, and placebo. The spatial distribution of the peak minima and maxima and the chosen regions of interests are shown in figure 2A. For both N20 and P25, a tangential dipolar topography was obtained indicating a near central cortex origin contralateral to the stimulation site. No significant changes of the peak-to-peak amplitude $A_{N20\text{-}P25}$ were observed after infusion of remifentanil, propofol, or placebo (figs. 2B and C). Moreover, no significant correlations were found between changes of the early SSEP components and changes in

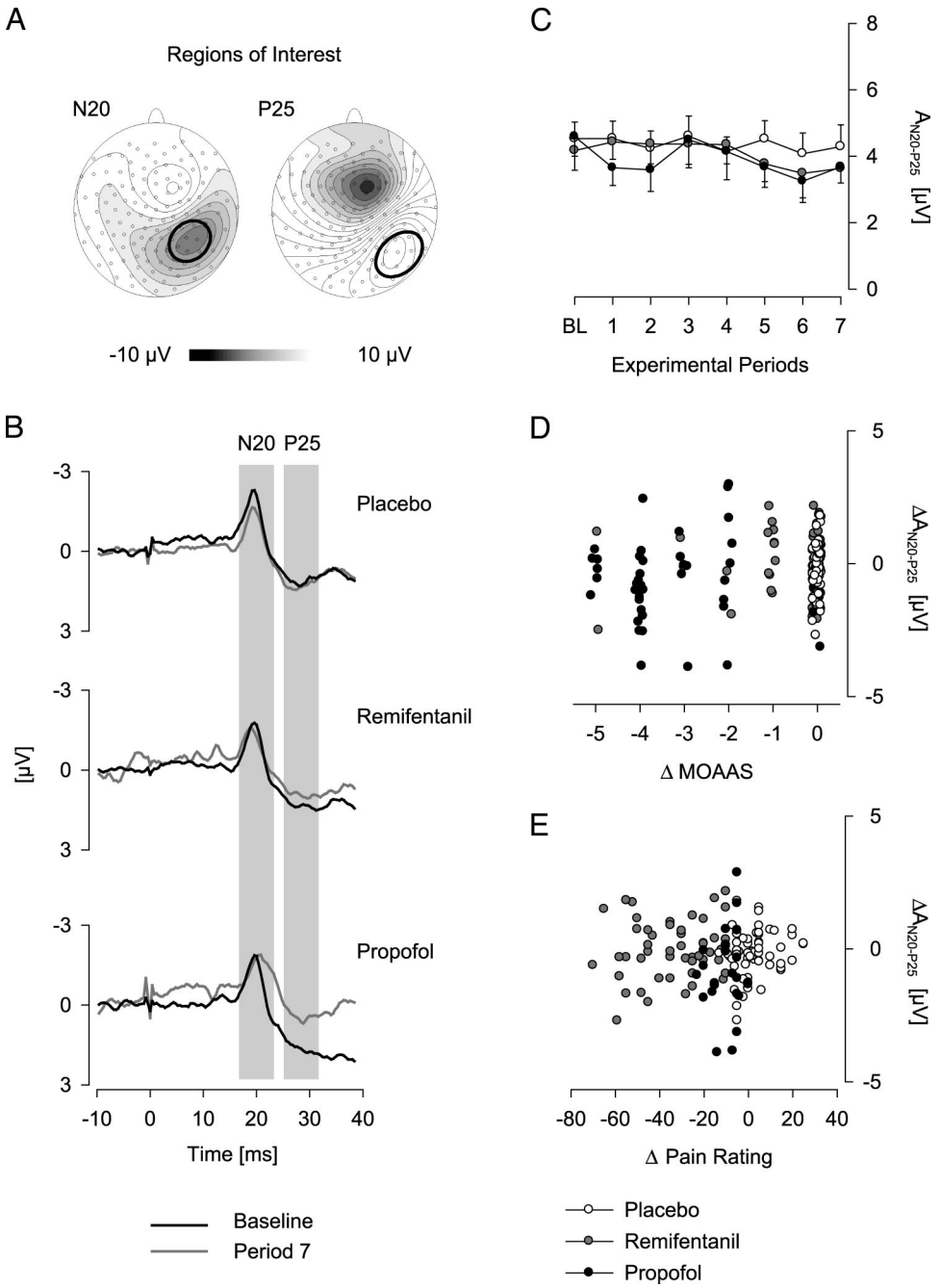

Fig. 2. Early components after median nerve stimulation (SSEP). (*A*) Spatial distribution of the N20 and P25 amplitude for one subject and the surrounding region of interest. (*B*) Grand averages (region of interest for N20) for placebo, remifentanil, and propofol for the baseline (*black line*) and final experimental period (*gray line*). *Gray regions* mark the windows for peak detection. (*C*) Mean and SE of the N20-P25 amplitude difference before (baseline [BL]) and during stepwise increase (experimental periods 1–7) of placebo (*white circles*), remifentanil (*gray circles*), and propofol (*black circles*). * Statistically significant changes relative to baseline ($P < 0.05$). (*D*) Correlation between changes in $A_{N20-P25}$ and sedation (modified Observer's Assessment of Alertness and Sedation Scale [MOAAS]). Notice that the circles were slightly scattered around the respective MOAAS values to improve readability. (*E*) Correlation between changes in $A_{N20-P25}$ and pain ratings.

pain perception ($r = 0.02$, $P > 0.05$) and MOAAS ($r = 0.09$, $P > 0.05$; figs. 2D and E).

Late Components of SSEP

Remifentanil and propofol differed profoundly in their effects on the late SSEP components P50 and N150. The spatial distribution of the peak minima and maxima and the chosen regions of interests are shown in figure 3A. As illustrated in figures 3B and C, the peak-to-peak amplitude $A_{P50-N150}$ significantly increased in the remifentanil group. In contrast, in the propofol and placebo group, the amplitude $A_{P50-N150}$ was not significantly affected (figs. 3B and C). Moreover, changes in $A_{P50-N150}$ were highly significantly correlated with changes in pain

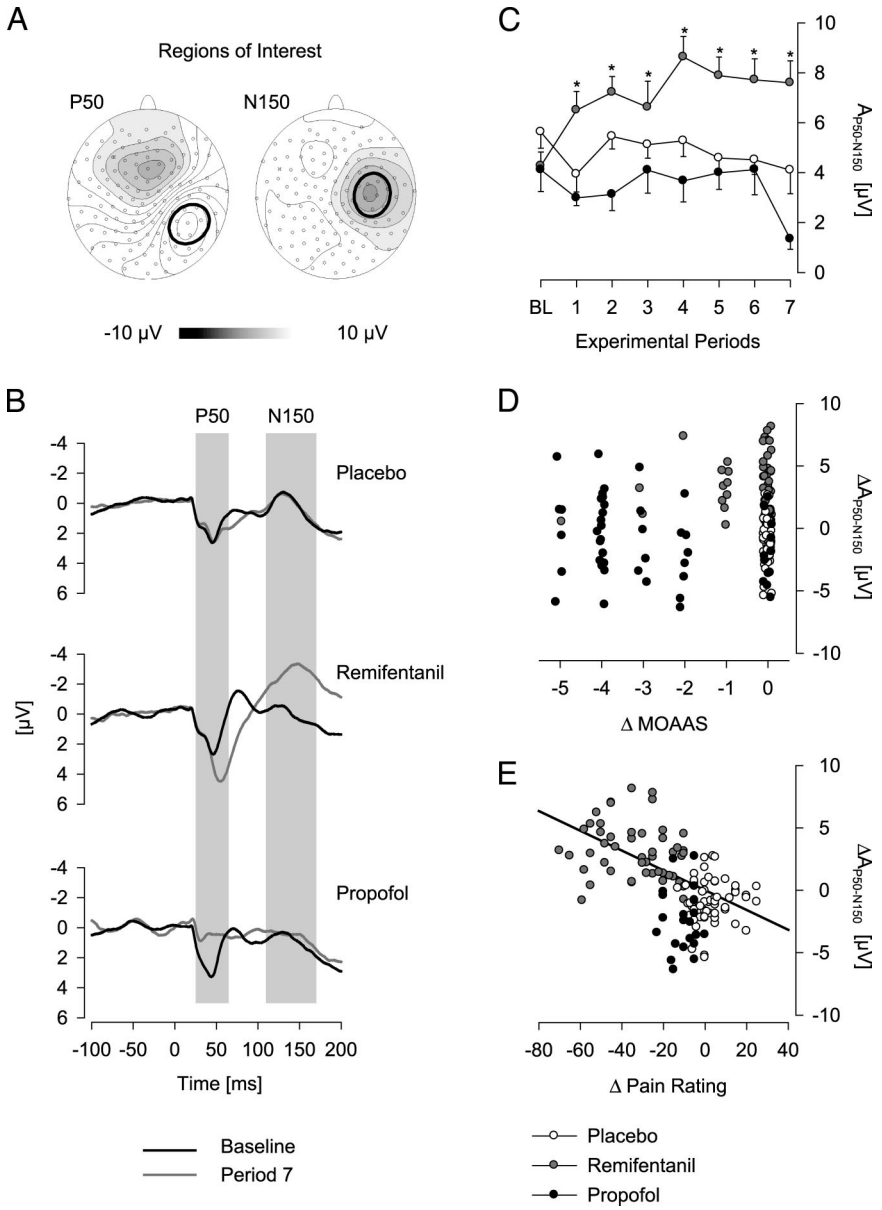

Fig. 3. Late components after median nerve stimulation (SSEP). (*A*) Spatial distribution of the P50 and N150 amplitudes for one subject and the surrounding region of interest. (*B*) Grand averages (region of interest for P50) for placebo, remifentanil, and propofol for the baseline (*black line*) and final experimental period (*gray line*). *Gray regions* mark the windows for peak detection. (*C*) Mean and SE of the P50-N150 amplitude difference before (baseline [BL]) and during stepwise increase (experimental periods 1–7) of placebo (*white circles*), remifentanil (*gray circles*), and propofol (*black circles*). * Statistically significant changes relative to baseline ($P < 0.05$). (*D*) Correlation between changes in $A_{P50-N150}$ and pain sedation (modified Observer's Assessment of Alertness and Sedation Scale [MOAAS]). Notice that the circles were slightly scattered around the respective MOAAS values to improve their readability. (*E*) Correlation between changes in $A_{P50-N150}$ and pain ratings.

perception ($r = -0.57$, $P < 0.001$), whereas no significant correlation was found with changes in sedation as assessed by MOAAS ($r = 0.06$, $P > 0.05$; figs. 3D and E).

Intracutaneous SEP

No early components could be detected after intracutaneous stimulation. However, late components N150 and P260 were identified for the iSEP (fig. 4). The spatial distribution of the peak minima and maxima and the chosen regions of interests are shown in figure 4A. The peak-to-peak amplitude $A_{N150-P260}$ decreased significantly with remifentanil and with propofol (figs. 4B and C). Changes in $A_{N150-P260}$ were significantly correlated with changes in pain ratings ($r = 0.61$, $P < 0.001$) and MOAAS ($r = 0.24$, $P < 0.01$; figs. 4D and E).

Discussion

In the current study, high-density electroencephalographic recordings were performed in 10 volunteers during stepwise application of remifentanil and propo-

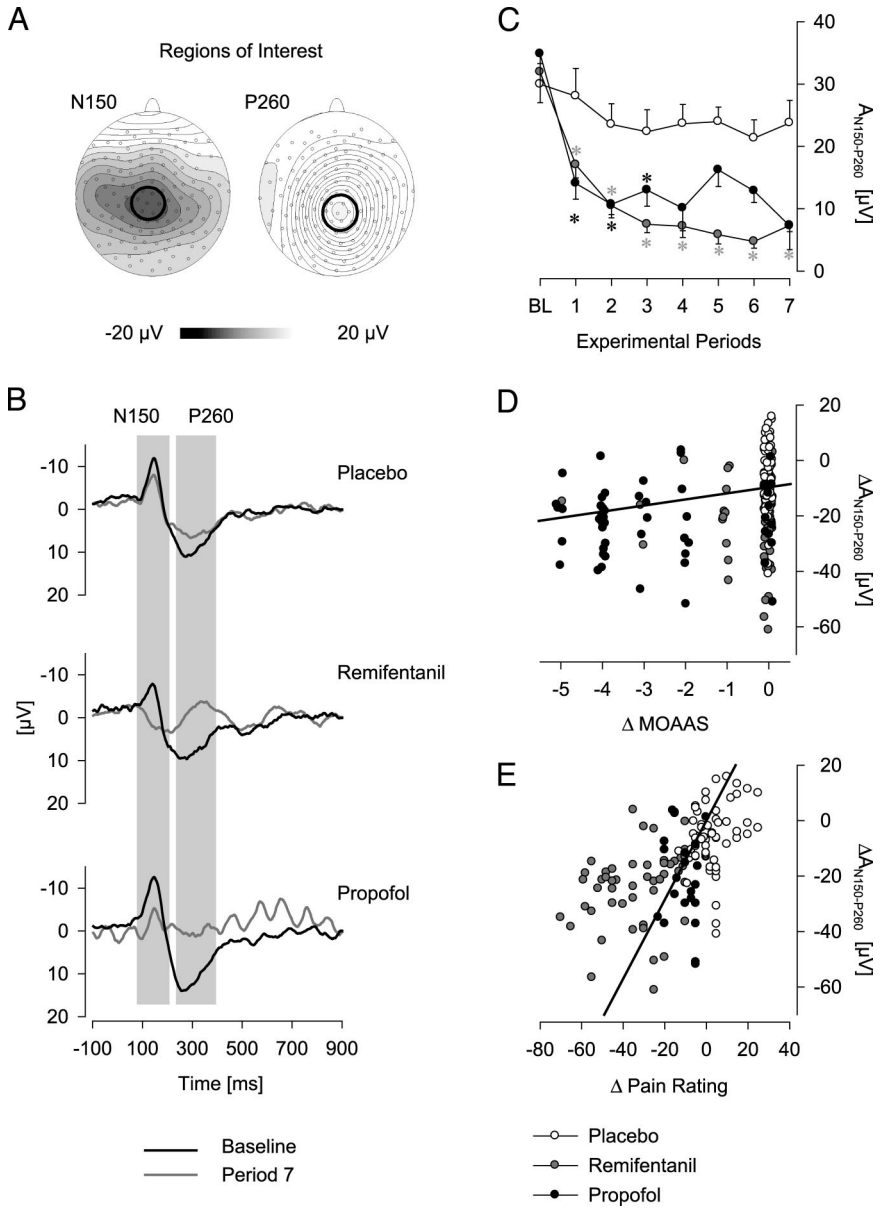

Fig. 4. Late component of intracutaneous evoked potential (iSEP). (*A*) Spatial distribution of the N150 and P260 amplitudes for one subject and the surrounding region of interest. (*B*) Grand averages (region of interest for N150) for placebo, remifentanil, and propofol for the baseline (*black line*) and final experimental period (*gray line*). *Gray regions* mark the windows for peak detection. (*C*) Mean and SE of the N150-P260 amplitude difference before (baseline [BL]) and during stepwise increase (experimental periods 1–7) of placebo (*white circles*), remifentanil (*gray circles*), and propofol (*black circles*). * Statistically significant changes relative to baseline. (*D*) Correlation between changes in $A_{N150-P260}$ and sedation (modified Observer's Assessment of Alertness and Sedation Scale [MOAAS]). Notice that the circles were slightly scattered around the respective MOAAS values to improve readability. (*E*) Correlation between changes in $A_{N150-P260}$ and pain ratings.

fol. Using evoked potentials, we aimed to disentangle the analgesic and hypnotic components of these anesthetics. Evidently, sedation and analgesia are not necessarily independent. Opioids such as remifentanil are well known to also show a sedative effect, and hypnotics such as propofol interfere with conscious processing of painful stimuli. However, in the current study, remifentanil induced a strong analgesic effect without relevant sedation. In contrast, propofol caused a profound sedation with only a moderate analgesic effect.

To identify an electroencephalographic indicator of the nociceptive blockade during anesthesia, we searched for a parameter that differentiates between the effects of remifentanil and propofol. These criteria were met by the late components P50 and N150 SSEP recorded after median nerve stimulation. With remifentanil, the amplitude $A_{P50-N150}$ increased significantly, whereas $A_{P50-N150}$ decreased with propofol. $A_{P50-N150}$ was unchanged in the placebo condition. Moreover, the changes in $A_{P50-N150}$ correlated highly significantly with changes in subjective pain perception while being uncorrelated with the level of sedation, as assessed by MOAAS.

Interestingly, we found that SSEP amplitudes were increased and not reduced by remifentanil. To our knowledge, effects of remifentanil on the late components P50 and N150 have not yet been reported. Crabb *et al.*[22] investigated the components P25-N35 and N35-P45. After remifentanil application, these components increased significantly. The authors discussed a decrease in depth of anesthesia caused by factors such as reducing blood concentration of propofol, discomfort of the laryngeal mask and arterial pressure cuff. In the current study, no significant changes in sedation were found in the remifentanil group. Therefore, our findings support the hypothesis that remifentanil can cause increased late SSEP amplitudes. Etomidate is known to induce still higher increases in amplitudes, which may be due to an increased synchronization or altered equilibration between inhibitory and excitatory cortical networks.[23] Based on our findings, we suggest that the differences in late SSEP components observed between remifentanil and propofol may reflect the nociceptive blockade induced by remifentanil. If so, these components could provide specific additional information to monitor the depth of anesthesia. However, further studies are needed to fully investigate the potential of late SSEP during general anesthesia and remifentanil.

In the current study, no changes of the early components of SSEP were found. This is in contrast to Thornton *et al.*,[24] who argue that the pontine–thalamic components (P15-N20) of the SSEP can specifically measure the nociceptive block of balanced anesthesia. In contrast to isoflurane, nitrous oxide profoundly depresses the amplitude P15-N20,[24,25] in accordance with its well-known nociceptive potency. The opioid alfentanil can decrease the amplitude of N20 in a dose-dependent manner. This effect was antagonized by naloxone.[26] Crabb *et al.*[22] demonstrated that remifentanil during isoflurane anesthesia decreased the amplitude P15-N20. These effects were not dose related. Interestingly, the amplitudes of the respective reductions were more pronounced after fentanyl as compared with remifentanil. To the best of our knowledge, our study is the first investigating SSEP during remifentanil without other anesthetics. It seems plausible that the decrease of early SSEP amplitudes in the above-cited studies may be due to an interaction of opioids and volatile anesthetics.

Bromm *et al.* demonstrated the advantage of intracutaneous (iSEP) over transdermal stimulation because of the more selective stimulation of nociceptive Aδ- and C-fibers.[16,17] In accordance with the literature, no early iSEP components were found in the current study. However, we identified late iSEP components N150 and P260 which were significantly reduced by remifentanil. Moreover, a highly significant correlation was found between changes in pain perception and these late iSEP components. Kochs *et al.*[18] reported the possibility to quantify pain perception after application of ketamine with the late components of the iSEP. They obtained a correlation coefficient of $r = 0.61$ between changes in pain perception and changes in amplitude of late iSEP components, which is remarkably similar to our observations. However, in the current study, propofol also markedly reduced the amplitude of late iSEP components, although inducing only a moderate decrease of subjective pain perception. After higher dosage of propofol, the iSEP became even undetectable. This pattern of results underlines the dependency of the late iSEP on the level of sedation. In addition to analgesics, a decrease in vigilance may also reduce the perception of pain. This could explain why the late components of iSEP do not specifically reflect the nociceptive blockade during anesthesia. In accordance with our findings, Meissner *et al.*,[27] who investigated the effects of acupuncture during propofol sedation, were unable to reliably identify the N150 amplitude during propofol anesthesia.

However, some methodical limitations should be recognized. In the current study, the subject's responsiveness after pain rating was assessed with the MOAAS. The assessment of sedation was performed immediately after pain stimuli. Therefore, painful stimuli might serve as an arousal stimulus and would decrease the level of sedation. For that reason, the chosen approach may not detect levels of light sedation. It remains unclear whether a light level of sedation would reduce pain perception, even if the sedative effect is antagonized by painful stimuli.

Taken together, the current study demonstrates that only the late components of the SSEP seem able to discriminate between the analgesic effect induced by remifentanil and the sedation induced by propofol. Further studies are needed to clarify whether late SSEP components can be routinely used to specifically monitor the depth of analgesia during general anesthesia.

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