Anesthesia Prevents Auditory Perceptual Learning

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Background: An auditory perceptual learning paradigm was used to investigate whether implicit memories are formed during general anesthesia.

Methods: Eighty-seven patients who had an American Society of Anesthesiologists physical status of I–III and were scheduled to undergo an elective surgery with general anesthesia were randomly assigned to one of two groups. One group received auditory stimulation during surgery, whereas the other did not. The auditory stimulation consisted of pure tones presented via headphones. The Bispectral Index level was maintained between 40 and 50 during surgery. To assess learning, patients performed an auditory frequency discrimination task after surgery, and comparisons were made between the groups. General anesthesia was induced with thiopental and maintained with a mixture of fentanyl and sevoflurane.

Results: There was no difference in the amount of learning between the two groups (mean ± SD improvement: stimulated patients 9.2 ± 11.3 Hz, controls 9.4 ± 14.1 Hz). There was also no difference in initial thresholds (mean ± SD initial thresholds: stimulated patients 31.1 ± 33.4 Hz, controls 28.4 ± 34.2 Hz). These results suggest that perceptual learning was not induced during anesthesia. No correlation between the bispectral index and the initial level of performance was found (Pearson r = −0.09, P = 0.59).

Conclusion: Perceptual learning was not induced by repetitive auditory stimulation during anesthesia. This result may indicate that perceptual learning requires top-down processing, which is suppressed by the anesthetic.

GENERAL anesthesia (GA) suppresses conscious perception. However, the brain is not completely shut down during anesthesia. For example, sensory stimulation still evokes a strong first wave of cortical activation. Even after a century of research, it is still largely unknown to what extent stimulation can induce learning and memory. For example, words presented during GA influence postsurgery reading performance and word-stem completion. However, it remains unknown whether the underlying learning is implicit or related to explicit learning during short periods of “lighter” anesthesia.

A reliable paradigm to investigate implicit learning is perceptual learning. In perceptual learning, repetitive stimulation with the same stimuli, e.g., two tones, which are hard to discriminate, yields improvement of performance, i.e., it becomes easier to discriminate the two tones. With this training, performance improves slowly in hundreds of stimuli presentations. Hence, learning is not caused by very few presentations of stimuli, as is the case with, for example, word stem completion. Crucial for the current study is that perceptual learning occurs in awake, healthy participants also when the stimuli are unattended or subliminal. For example, Amitay et al. presented tones of different frequencies to participants who performed tasks unrelated to the tones (e.g., reading a book). Even though the tones were not attended, the passive stimulation improved the frequency discrimination of the tones. Therefore, the mere presentation of tones induced learning in these passive participants. Analogous results were also found in the visual domain, even with subliminal stimuli.

Hence, if repetitive stimulation with unattended and subliminal stimuli is sufficient to provoke implicit learning in healthy, awake participants, it may also be possible to induce perceptual learning during GA.

To test this hypothesis, a group of anesthetized patients received auditory stimulation during surgery, whereas another group did not. Both groups performed an auditory frequency discrimination task after the surgery, and the performance of the groups was compared. If perceptual learning can be induced during GA, the group that received stimulation during surgery would perform the task better, as compared with the control group. If GA prevents perceptual learning, there should be no difference in performance between the groups. We found the latter to be true.

Materials and Methods

Patients

The study was approved by the local institutional ethics committee (University of Lausanne, Lausanne, Vaud, Switzerland). Patients who had an American Society of Anesthesiologists physical status of I–III and were aged 19–61 yr were recruited and provided informed written consent. These patients underwent vascular or orthopedic surgery during GA lasting for more than 60 min. In the preoperative phase, potential participants were tested to make sure they were eligible for the study. Exclusion criteria were hearing deficits, neurologic pathology, chronic alcoholism, a history of drug abuse, and treatment with benzodiazepines, neuroleptics, antidepressants, or antiepileptics, as well as not comprehending the task with very easy stimuli or having a hearing deficit.

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threshold above 30 dB for detecting a pure tone of 1 kHz. To investigate whether musical expertise had any influence on learning, patients had to indicate for how long they had played a musical instrument. Finally, 87 patients fulfilled the above criteria and were randomly assigned to one of two groups based on a premade list of patients. One of the groups received auditory stimulation during surgery, whereas the other, the control group, did not. A list was created by concatenating smaller lists containing 10 patients. In each of these lists, patients were randomly assigned to receive stimulation (n = 5) or to be controls (n = 5). The 1st list contained patients 1–10, the 2nd list contained patients 11–20, and so on.

In a pilot study, eight paid students from the Ecole Polytechnique Fédérale de Lausanne (Lausanne, Switzerland) were recruited (and performed the learning experiment without GA).

General Procedure
A schematic of the general procedure is illustrated in figure 1. Patients were told they would be placed randomly in one of two groups, and that one of these groups would receive auditory stimulation during the surgery. On the day of surgery, presentation of stimuli was initiated (for the stimulated group only) as soon as the Bispectral Index (BIS) value was between 40 and 50. After recovery, usually 24–48 h after surgery, all patients performed 10 blocks of the frequency discrimination task.

Anesthetic Procedure
After arrival in the operating room, standard monitoring was applied. The forehead skin was cleaned with ether to improve skin conductance, and the BIS XP-Sensor® electrodes (Aspect Medical Systems, Newton, MA) were applied as recommended by the manufacturer. The electroencephalogram was recorded continuously using the Aspect A-2000 BIS® monitor (version XP).

After preoxygenation with 100% oxygen, anesthesia was induced with 2–3 mcg/kg fentanyl, 3–6 mg/kg thiopental, and 0.1 mg/kg vecuronium. All patients were intubated by the oral route. Anesthesia was maintained with fentanyl, a mixture of air and oxygen, sevoflurane, and vecuronium if necessary. The in-charge physician was requested to maintain a BIS value between 40 and 50.

Intrasurgical Stimulation (Stimulated Group)
During each trial, two pure tones of 100 ms with 20 ms cosine rise/fall were presented in two intervals 500 ms apart. Tones were presented at 80 dB. One of the tones had a frequency of 1 kHz, whereas the other had a frequency of 1 kHz + Δf (with Δf being 1, 4, 16, or 64 Hz). The reference tone of 1 kHz was presented randomly in the first or the second interval. In each trial, one of the four levels of Δf was chosen randomly. All levels of Δf were presented equally many times. In total, patients were presented with 1,000 pairs of tones during surgery. Each such trial was separated by 1,500 ms. The entire stimulation lasted approximately 30 min. In a pilot study, perceptual learning was successfully induced in healthy students when using this paradigm (fig. 2A). Crucial for this study, passive stimulation with pure tones induced learning in a frequency discrimination task for awake participants.

Postsurgical Discrimination Task (Stimulated and Control Groups)
In the postsurgical frequency discrimination task, participants fixated a white cross in the middle of a screen while auditory stimuli were presented via headphones. Stimulation was identical to the intrasurgical stimulation, except that Δf was varied using an adaptive staircase method. The task of the participants was to determine whether the tone with the higher frequency (1 kHz + Δf) was presented in the first (fig. 1A) or the second interval (fig. 1A). Participants responded by pressing one

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**Fig. 1.** Stimuli and procedure. (A) A pure tone of 1 kHz is presented, followed by a pure tone of 1 kHz + Δf. (B) A pure tone of 1 kHz + Δf is presented, followed by a pure tone of 1 kHz. Δf varied according to the QUEST procedure. (C) Both groups performed the initial screening procedures and underwent surgery during anesthesia. Only one group received auditory stimulation during the surgery. After surgery, both groups performed 10 blocks of the frequency discrimination task. (D) Procedure used to calculate the dependent variables. When analyzing differences in amount of learning, the mean of the thresholds for the first five blocks and the mean of the thresholds for the last five blocks were calculated (T1 and T2, respectively). For comparing initial performance levels, the mean of the first three thresholds was calculated for each patient. A hypothetic learning curve is shown; decreasing performance levels indicate learning.
proved quickly. Averaged data. With this paradigm, performance im-
above 200 Hz were excluded to avoid outliers in the 
participants can discriminate smaller 
when the discrimination threshold becomes smaller ( 
thresholds greater than 100 Hz did not significantly 
difference in frequency, of 10 min after the fifth block. By adaptively varying the 
blocks of 100 trials each. There was a mandatory pause 
in green and red letters, respectively) was pro-
Wrong 
determination test assumes that the null hypothesis is true (i.e., 
change the correlation ( 
subjects. All three groups improved performance compar-
and last five blocks for the patient groups only. There is no 
difference in performance between the stimulated and control 
patients improved performance com-
A 
forced after each response. Participants performed 10 
blocks of 100 trials each. There was a mandatory pause of 10 min after the fifth block. By adaptively varying the difference in frequency, \( \Delta f \), a discrimination threshold could be determined for each block. Learning occurs when the discrimination threshold becomes smaller (i.e., participants can discriminate smaller \( \Delta f \)). Thresholds above 200 Hz were excluded to avoid outliers in the averaged data. With this paradigm, performance improved quickly. 

Auditory Equipment

For the auditory stimulation before, during, and after surgery, tones were presented via closed headphones (Sennheiser HD 280 Pro; Sennheiser electronic GmbH & Co. KG, Wennebostel, Germany) connected to a laptop computer (Dell Latitude D410; Dell Inc., Austin, TX).

Data Analysis of Perceptual Learning

For each block, a discrimination threshold was deter-
moved by fitting a cumulative gaussian function to the 
characteristics are shown in table 1.

Results

One hundred four patients were initially included in 
underwent a surgical procedure with GA. Thirteen patients declined to perform the postsurgical testing. Two more patients were excluded because of failure of performing the frequency discrimination task, and another two patients were excluded because of software failures. Therefore, 87 patients completed the study. Eighty-five percent of the BIS readings fell into the intended range (BIS 40–50), suggesting that patients were under deep anesthesia during stimulation. Patient characteristics are shown in table 1.

Learning curves and mean thresholds are shown in 
figures 2A and B. Participants in the pilot study improved
performance with training ($P < 0.01$). To investigate differences in the amount of learning for the patient groups, a two-way mixed-factors analysis of variance with factors Group and Time was calculated (fig. 2B). There was a main effect of Time ($F_{1,85} = 45.4, P < 0.0001$) but no main effect of Group ($F_{1,85} = 0.01, P = 0.91$). The interaction Group $\times$ Time was not significant ($F_{1,85} = 0.01, P = 0.94$). Hence, both groups of patients improved performance significantly in the frequency discrimination task. Because the performance of both groups was comparable (fig. 2B), the amount of learning was not influenced by the auditory stimulation during surgery.

This argument is also supported by the fact that the initial performance levels of both groups are roughly the same (fig. 2C). If the stimulation during surgery had induced learning, the initial performance of the stimulated group should be better compared with the control group. However, there was no difference in initial thresholds (mean initial threshold stimulated = 31.1 Hz, controls = 28.4 Hz; $P = 0.72$; fig. 2C).

It has been reported that implicit learning is correlated with the level of anesthesia. Patients with lighter levels of anesthesia improved performance more strongly.\textsuperscript{2,9} To investigate the relation between the level of anesthesia and perceptual learning, the correlation between the initial performance and the BIS values was calculated for the stimulated patients only. Three patients were excluded because of initial thresholds being larger than 100 Hz (fig. 2D). There was no significant correlation, suggesting the level of anesthesia had no influence on the amount of learning (fig. 2D, solid line; Pearson $r = -0.09, P = 0.59$); if the patients with initial thresholds larger than 100 Hz were included in the analysis, correlations were still not significant; fig. 2D, dashed line; Pearson $r = -0.17, P = 0.25$).

In auditory perceptual learning, improvement of performance is not always specific to the trained stimuli.\textsuperscript{23} Therefore, patients with musical experience might already be experts in performing the task. Indeed, the initial performance level of patients with at least 1 yr of practice playing a musical instrument was significantly better compared with patients without musical experience (fig. 3A; mean initial threshold musical experience = 15.1 Hz, no musical experience = 43.3 Hz; two-tailed permutation test: $P < 0.00001$). To conclude that the previous results were not due to ceiling effects of patients with musical experience, an additional analysis was performed only for patients reporting having no musical experience (patients who reported never having practiced playing an instrument). Figure 3B shows the thresholds for the first and second parts of the experiment (i.e., T1 and T2) for patients with no musical experience. A two-way analysis of variance with factors Group and Time was calculated for patients with no musical experience. There was a main effect of Time ($F_{1,43} = 43.5, P < 0.0001$) but no main effect of Group ($F_{1,43} = 0.01, P = 0.94$) or any significant interaction Group $\times$ Time ($F_{1,43} = 0.29, P = 0.59$). Therefore, both groups improved performance when performing the frequency discrimination task, and there was no difference in the amount of improvement between groups. To compare initial thresholds, a two-tailed permutation test was conducted on the initial performance. Again, there was no difference in initial thresholds.

### Table 1. Demographic Data

<table>
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<th></th>
<th>Stimulated</th>
<th>Controls</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>49</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>40.3 ± 11.1</td>
<td>41.9 ± 10.4</td>
<td>0.33</td>
</tr>
<tr>
<td>BIS</td>
<td>42.1 ± 6.4</td>
<td>42.3 ± 7.2</td>
<td>0.82</td>
</tr>
<tr>
<td>Muscular experience, n</td>
<td>5.7 ± 10.0</td>
<td>4.0 ± 9.1</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. There were no significant differences ($P > 0.05$) in demographic data between the two groups, as investigated by two-tailed permutation tests.

BIS = Bispectral Index.

![Fig. 3. Performance on the frequency discrimination task for patients without any musical experience (mean ± SD).](image)

(A) Initial performance for patients with at least 1 yr of musical experience and patients with no (less than 1 yr) musical experience. The initial performance level of musical experienced patients is significantly better compared with patients with no musical experience. (B) The improvement of performance in the frequency discrimination task for patients with no musical experience. There is no difference in performance between the stimulated and control groups. (C) Initial performance of stimulated and nonstimulated patients with no musical experience. There is no difference in initial performance, suggesting that auditory stimulation did not induce perceptual learning. (D) Correlation between the initial performance and level of anesthesia (Bispectral Index [BIS]) for patients with no musical experience (solid line). The correlation was not significant. Including three outliers with initial thresholds greater than 100 Hz did not change the correlation significantly (dashed line).
(fig. 3C; mean initial threshold stimulated = 44.6 Hz, controls = 41.4 Hz; \( P = 0.80 \)). In addition, there was no significant correlation between the initial performance and the level of anesthesia (fig. 3D, solid line; Pearson \( r = -0.05, P = 0.83 \); including the three patients with initial thresholds above 100 Hz did not change the results; fig. 3D, dashed line; Pearson \( r = -0.21, P = 0.30 \)).

**Discussion**

Perceptual learning is a form of long-term implicit learning lasting for years.\(^2\) Perceptual learning can be induced by subliminal stimuli in healthy, awake participants,\(^3\) e.g., when paired with another task\(^4\) or even with a reward signal only.\(^5\) Moreover, perceptual learning can be induced without attending to stimuli, i.e., passive stimulation.\(^6\) For example, repetitive stimulation of pure tones with the same stimulus paradigm successfully induced perceptual learning in awake, healthy participants performing a different task.\(^7\) Hence, we hypothesized that repetitive stimulation during GA may also induce perceptual learning. However, this was not the case. Overall, both patient groups improved performance equally on the postsurgical frequency discrimination task (figs. 2A and B). Also, the initial performance level was comparable between the groups (figs. 2B and C). Therefore, repetitive, auditory stimulation during anesthesia did not induce perceptual learning.

**Awareness of Stimuli**

Learning might be related to the level of anesthesia and awareness of stimuli.\(^2\)\(^,\)\(^4\)\(^,\)\(^6\)\(^,\)\(^8\)\(^,\)\(^9\) Only a BIS level above 40 enabled formation of implicit memories in a word-stem completion task\(^3\) and similar results were found in a speed-reading task.\(^2\) In contrast, no significant relation between the level of anesthesia (BIS) and the initial performance levels was found in the current study (figs. 2D and 3D).

It has been suggested that during GA, patients are unaware of the stimuli and are therefore unable to form memories.\(^3\) However, perceptual learning can be induced even when awake participants are unaware of the stimulation.\(^4\)\(^,\)\(^5\) In addition, cortical plasticity can be induced by repetitive stimulation during anesthesia in rats.\(^6\) Therefore, being unaware of the stimulation alone cannot explain why perceptual learning was not induced in the current study. Hence, GA might suppress perceptual learning itself or its consolidation.\(^7\)

**Postsurgical Conditions**

In general, learning occurs already as training proceeds, i.e., it does not only show up after consolidation. This is evident also in the current study (figs. 2A and B; see also Amitay et al.\(^8\) and Hawkey et al.\(^5\)). Still, there is the possibility that successful learning, induced during GA, was erased by postsurgical conditions such as stress and sleep deprivation. However, although stress might have a profound effect on learning,\(^8\) implicit learning is not sensitive to stress.\(^9\)\(^,\)\(^10\) Furthermore, although sleep might be crucial for visual perceptual learning,\(^11\)\(^,\)\(^12\) this is not the case for auditory learning.\(^13\)\(^,\)\(^14\)\(^,\)\(^15\) Hence, it seems that perceptual learning was obliterated because of GA itself and not postsurgical conditions.\(^7\)

**Specificity and Nonspecificity of Perceptual Learning**

Various studies show that GA influences the neural response in a nonspecific way.\(^16\)\(^,\)\(^17\) Therefore, stimulation during GA might trigger different neural populations compared with the postsurgery testing. Perceptual learning is often very specific to the basic characteristics of the trained stimuli.\(^18\)\(^,\)\(^19\) Hence, if different neural populations are triggered during GA compared with the awake state, plastic changes induced by the stimulation may not be beneficial in the awake state, i.e., when performing a postsurgical task. However, the stimuli used in the current study are known to transfer across broad frequency bands, i.e., they are less specific than normal visual stimuli (for this reason they were chosen in this study). Moreover, cortical plasticity was induced in rats with GA.\(^16\)

**Recurrence Processing**

It has been suggested that consciousness relies on bidirectional integration of sensory information\(^1\)\(^,\)\(^28\)\(^,\)\(^30\)\(^,\)\(^31\) and that the cause of anesthetic-induced unconsciousness is an alteration of the information flow between higher-order areas and areas processing basic sensory information.\(^1\)\(^,\)\(^32\)\(^,\)\(^33\) For example, GA reduces the information flow from frontal to posterior areas but preserves it from posterior to frontal areas.\(^34\)\(^,\)\(^35\) Therefore, feed forward processing of stimuli seems to be intact during GA, whereas top-down processing is disrupted. Top-down influences have profound effects on perceptual learning and cortical plasticity.\(^36\)\(^,\)\(^37\) Something also acknowledged by computational models.\(^38\)\(^,\)\(^39\) Importantly, also perceptual learning without awareness of stimuli seems to rely on top-down influences, e.g., in the form of reward processing and feedback\(^36\)\(^,\)\(^37\) (see introduction). Recently, it was shown that monkeys’ improvement on a visual task could be related to changes in the neural response in early visual areas.\(^40\) Interestingly, when the monkeys were anesthetized, there was no longer any difference in the neural response, thus suggesting that crucial top-down influences had been knocked out by the anesthetics.

Therefore, the reason why perceptual learning was not induced in the current study might be because of anesthetic-induced disabling of crucial top-down influences. Importantly, this account would still allow for perceptual priming to occur during anesthesia. For example,
the improvement of performance in a word-stem completion task is specific to the “primed” word, possibly occurring within bottom-up processing55 and immune to GA.56,57 However, these considerations remain speculations at the moment.

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