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Does implicit memory during anaesthesia persist in children?

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Background. Recent studies suggest that implicit memory (especially perceptual implicit memory) persists during adequate general anaesthesia in adults. Studies in children, however, have failed to demonstrate implicit memory during general anaesthesia, possibly because of differences in methodological design. We therefore designed a prospective study with the aim of evaluating implicit memory in children undergoing general anaesthesia, using a perceptual memory test based on the mere exposure effect, previously tested in a control group.

Methods. Twelve infrequent neutral words were played 12 times in a random sequence via headphones to 36 children aged 8–12 yr during elective or emergency surgery. The children were not premedicated, and general anaesthesia was maintained with isoflurane. The word presentation started immediately after the surgical incision. Within 36 h after the stimulus presentation, the memory was assessed by using a forced-choice preference judgement task. Time constraint and word deterioration with a low-pass filter were used to prevent the subjects from utilizing intentional retrieval. The implicit memory score was obtained by calculating the proportion of target words preferred, which was compared with the chance level (0.5).

Results. The percentage of correct responses given by the children was comparable with the chance level. The memory score was mean (SD) 0.48 (0.16) (95% CI 0.43–0.53).

Conclusions. The use of a perceptual implicit memory test based on the mere exposure procedure in children failed to reveal any evidence of implicit memory under general anaesthesia.

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Implicit memory implies the influence of past experience on a person's performance or behaviour that does not require intentional or conscious recollection of a prior learning episode.[1] Procedures for the study of implicit memory are classified into two groups: perceptual and conceptual implicit memory tasks. This distinction is made on the basis of the task's processing demands: in the first group, the performance involves the analysis of stimulus form (e.g. the identification of a word masked in background noise, or the generation of a word from a fragment), whereas in the second group, the performance involves the analysis of stimulus meaning (e.g. the production of a category exemplar).

Early studies of implicit learning during anaesthesia in adults produced conflicting results because of the lack of standardization of the methodology.[2 3] However, recent studies with control of the depth of anaesthesia have furnished evidence that implicit memory persists in adults, even at an adequate level of anaesthesia.[4] Moreover, it has been suggested that only one form of implicit memory, perceptual implicit memory, persists during adequate general anaesthesia and can exist in the absence of conscious awareness.[5] Nonetheless, the psychological consequences of implicit memory during anaesthesia on the subsequent state of the patients have still not been characterized.

Intriguingly, implicit memory during anaesthesia has not been systematically investigated in children. Few early studies demonstrated no evidence of learning during general anaesthesia in children.[6–8] Many reasons may explain these negative results, such as the lack of a control group, which is essential for the verification of the adequacy of the test to detect implicit memory, and the use of conceptual implicit memory tests that are known to be less persisting than perceptual processing during anaesthesia. Moreover, the use of benzodiazepines for premedication may have contributed to the absence of implicit memory.[9] A very recent study conducted in a large group of children that used an adequate perceptual implicit memory test pretested on a control group failed to demonstrate any evidence of implicit memory in the anaesthetized group.[10] Given these sparse findings, further studies with the application of different perceptual implicit memory tests are still needed before categorical conclusions can be drawn concerning the absence of implicit memory under general anaesthesia in children.

In an attempt to investigate the role of the type of test in the detection of implicit memory in children undergoing general anaesthesia, we designed a prospective study that involved a perceptual implicit memory task different from that applied by Andrade and colleagues.[10] Accordingly, we explored implicit memory during general anaesthesia in unpremedicated children admitted for elective or emergency surgery, through the use of a perceptual memory test based on the mere exposure effect, previously tested in a control group.

Methods

After approval by our University Hospital Ethics Committee and written informed consent from the parents and the children, we enrolled into the study 38 children, aged between 8 and 12 yr, ASA I or II, who had been admitted for elective or emergency surgery under general anaesthesia. Children who had a diagnosis of hearing defect, who did not speak French fluently, or who had a pathology that could affect cognitive functions were excluded from the study. In addition, we did not include any child undergoing adenotonsillectomy to preclude any hearing problem that may occur in these patients.

All the patients received acetaminophen 20 mg kg^{-1} 30 min before the operation. At the time of arrival in the operating room, the patients were monitored using ECG, pulse oximeter, non-invasive blood pressure monitor, and a precordial stethoscope. The induction of anaesthesia was left at the discretion of the anaesthesiologist with either mask induction with sevoflurane or i.v. induction with propofol depending on the child's preference and our routine practice. The airways were maintained by a laryngeal mask or a tracheal intubation (after the administration of atracurium 0.5 mg kg^{-1}). Analgesia and maintenance of anaesthesia were standardized in all children with the administration of fentanyl (up to 3 $\mu g\ kg^{-1}$) and isoflurane (1 MAC) in a mixture of 50% O_2 in air or N_2O. In some cases, regional anaesthesia was performed for the postoperative analgesia.

The task consisted of the presentation of spoken words immediately after the surgical incision, followed by a preference task testing the implicit memory of these words during a postoperative evaluation within 36 h after the presentation of the stimuli.

The stimuli comprised 36 neutral French words, which were nouns, verbs, or adjectives. They had similar lexical characteristics, the same length (three syllables), and a low but equal distribution of frequency of occurrence in the French language.[11] These 36 words were divided into three lists of 12 words. Each list was read out by a different woman. The sound level was normalized by using Sonic Foundry Sound Forge 4.5 (Sonic Foundry Inc.).

In the exposure phase, one list of 12 words was played to the children via headphones placed on their ears (the volume was identical for each child as it was adjusted during the pilot study), connected to a Compaq nx7010 personal portable computer, interfaced with E-Prime software version 1.0 (Psychology Software Tools Inc., Pittsburgh, PA, USA).[12]

The children were told that music would be played via their headphones during the operation and that an attentional test would be performed after their operation. The test was presented as an attentional task and not as a memory task. In this way it is possible to reduce the probability that the children consciously make a link between the two phases of the test, and thus reduce the use of conscious or intentional retrieval of the words. In the operating room, after the children had lost consciousness, headphones were placed on their ears. The presentation started immediately after the surgical incision. The words were pronounced slowly and were played 12 times in a random sequence that was different for each child, with a 2 s delay between each word. The duration of the task was 5 min. A psychologist, who was not involved in the anaesthesia management, was always present during the presentation of the words to ensure that it was performed without any interruptions. Three subject groups were formed in different versions of the test during this first phase, according to the three lists of words, each one pronounced exclusively by one voice (list I, voice 1; list II, voice 2; list III, voice 3).

In the test phase, a forced-choice preference judgement task was performed within 36 h after the presentation of the stimuli, when the children were comfortable enough to answer adequately. The children were first asked whether they explicitly remembered any intraoperative event. They were then presented with 12 pairs of words containing a target word (a word heard previously and pronounced by the same voice as during the exposure phase) and a distractor word (a novel word chosen from one of the alternative lists of words and pronounced by a novel voice never heard before). In this way, we could observe implicit memory because the memory effect could appear on words studied and on voice studied.

The task of the children consisted in saying which word they liked best. If the children asked how to make their choice, they were informed that judgement is subjective and individual and to trust to their first impression. Each pair of words (target and distractor) was presented in a random sequence that was different for each child. The target word could appear in the first or in the second position in a random sequence. The interval between the target word and the distractor word was ~1s. The children were asked to respond as quickly as they could in order to reduce the use of intentional retrieval. The experimenter then pressed the key corresponding to the child's response (1 or 2) and the next pair of words was played. Thus, the interval between each pair of words was determined by the child.

In this test phase, each word (target and distractor) was made more difficult to discern by means of a low-pass filter, using Wavelab 0.3 (Real Sound Processor Audio Database Multitrack 24-Bit Wave). A low-pass filter is a filter that passes low-frequency signals, but attenuates signals with frequencies higher than a chosen cut-off frequency (here 2000 Hz). In our test, each word was processed five times. Each processing ensures the deletion of 20 dB from frequencies >2000 Hz. This filter leaves the fundamental frequency and the prosodic contour information intact. Subjectively, words sound muffled and are difficult to recognize. This filter reduces the conceptual component of the information, but preserves its perceptual aspect.[13] Additionally, in this way it is possible to reduce the probability that the subject consciously makes a link between the two phases of the test, and thus reduces the use of intentional retrieval. As the words are obscured, the implicit memory could strongly lead the word previously heard to be more identifiable and thus pleasant.

There were 12 different versions of the task during this second phase, according to the three lists of words (for each of the three lists used in the first phase of the test as targets, two lists of words could be used as distractors) and to the three voices (each distractor list could be pronounced by two different voices). This phase of the test generally lasted <5 min.

In case of implicit memory, the target word heard previously was preferred to the distractor word. The implicit memory score was obtained by calculating the proportion of target words preferred. This score was compared with the choice attributable to chance (0.5, the probability of choosing the target word without having been presented with it before).

Pilot study

This task was first administered to a pilot group of unanaesthetized children in order to be sure that a mere exposure effect could be observed in this population. Twenty-nine unanaesthetized children, 8–12 yr old, attending public school, were recruited in various areas around our hospital and submitted to the same exclusion criteria as the hospitalized children. The same procedure as mentioned earlier was applied for the implicit memory test, except for the instructions given to the children and the number of presentation of the words during the exposure phase (five presentations instead of 12). The children were told that they would hear a series of uncommon words. They were not asked to perform any specific encoding task, but only to listen carefully to the stimuli. The proportion of target words preferred over the distractors [mean (SD)] was 0.61 (0.18) (95% CI 0.54–0.68), which was statistically greater than the chance level at 0.5 [$t(28)=3.3$, one-tailed, $P<0.05$].

Study in anaesthetized children

The children were randomized into 12 groups, corresponding to the 12 versions of the cognitive task; each group contained three children. Calculation of the sample size was based on the results of our pilot study. The results indicated that the mean mere exposure effect (the proportion of target words preferred) was 0.61 (0.18). Given a power of 0.8, an α-value of 0.05, and based on a one-tailed t-test, we needed 18 subjects. In order to facilitate the randomization of lists of words and to improve the size effect, 36 children were recruited.

The one-sample Student's t-test was used to compare the proportion of preferred target words with the level of chance. The two-tailed t-test for independent samples was applied to compare the age and memory scores between anaesthetized and unanaesthetized children. A Fisher's exact test served to compare the genders between the two groups. Statistical significance was accepted at the 5% level.

Results

The characteristics of the children and the surgical data of the anaesthetized children are presented in Table 1.

Table 1 Characteristics of the anaesthetized and unanaesthetized (pilot study) children and the surgical data of the anaesthetized children. Data are mean (range) or mean (SD)

	Anaesthetized (n=36)	**Unanaesthetized (n=29)**	**Fisher's exact test, t-test (P-value)**
Age (yr)	9.9 (8–12)	10.1 (8–12)	0.6
Height (cm)	138.1 (10)		
Weight (kg)	32.6 (7.1)		
Male/female (n)	9/27	14/15	0.06
Surgery			
Duration of anaesthesia (min)	120.4 (98)		
Duration of surgery (min)	76.3 (85.3)		
Elective/emergency surgery (n)	32/4		

There was no difference between the unanaesthetized and anaesthetized children in terms of age or gender.

The patients underwent orthopaedic (n=21), urological (n=10), abdominal (n=4), or skin (n=1) surgery. In 13 cases, anaesthesia was induced i.v. with propofol; the other patients underwent inhalation induction with sevoflurane. Anaesthesia was maintained with isoflurane in all the children. Nitrous oxide formed part of the anaesthesia management in 17 children. The airways were secured by a tracheal tube in 17 patients, with 14 of them receiving atracurium to facilitate insertion. The other patients were managed with a laryngeal mask, and finally, 12 children received regional analgesia for the postoperative period.

No patients manifested awareness or spontaneous recall either of intraoperative events or of the presented words. The mean proportion of target words preferred by the anaesthetized children [mean (SD)] was 0.48 (0.16) (95% CI 0.43–0.53). This memory score was equal to the level of chance and was smaller than the mean score for the unanaesthetized children [0.61 (0.18)], [$t(63)=-2.81$, two-tailed, $P<0.05$].

Discussion

This is the first reported study of the use of a perceptual implicit memory test based on the mere exposure procedure in children. We demonstrated that this test is consistent in detecting implicit memory when administered to school children selected from a normal population. On the contrary, the application of this test to comparable children of the same age who underwent general anaesthesia revealed no perceptual implicit memory effect.

The mere exposure effect is obtained when incidental exposure to initially novel stimuli results in a more affective judgement, that is, it increases the likelihood that stimuli that have been seen before will be favoured over non-presented items later during a preference judgement task.[14] This effect has proved to be a robust, reliable phenomenon that is observed in response to a variety of stimuli, with different procedures and in various populations.[15] A potent explanation for the mere exposure effect is that a prior encounter produces a processing facilitation (i.e. greater speed and ease with which this stimulus is perceived, which is one of the determinants of affective preference).[16] Moreover, a number of neuropsychological studies have demonstrated a normal mere exposure effect in amnesic or Alzheimer patients, despite a profound inability to recognize the exposed stimuli.[17 18] These findings offer a strong argument for postulating that the mere exposure effect is an implicit memory manifestation, independent of explicit memory.[19] The test used in the present study presents various advantages when compared with previous studies:[6–8] first, it relies on a robust phenomenon, the mere exposure effect; secondly, we used a procedure that promoted perceptual processing and reduced conceptual processing (the conceptual components of the information were reduced); thirdly, it does not imply a high level of language capacity; and fourthly, it reveals an implicit memory effect in a control group.

To the best of our knowledge, only four earlier studies have evaluated implicit memory during general anaesthesia in children.[6–8 10] However, some of these previous studies could be biased by the use of benzodiazepines as premedication.[6 8] Indeed, benzodiazepines are known to reduce implicit memory and more specifically perceptual implicit memory.[9 20] Although these results have previously been demonstrated only in adults, benzodiazepines probably have the same impact on the implicit memory in children, as perceptual implicit memory is characterized by developmental invariance.[21] Some other studies could be also limited in their assessment of implicit memory because implicit memory tasks were used without previous application in a control population of the same age.[6–8] Nevertheless, and similarly to what has been reported previously, we failed to demonstrate any evidence of implicit memory in children who underwent general anaesthesia despite the exclusion of any premedication and the presence of significant implicit memory effect in a control group.

Regarding the earlier studies, the type of memory tests used may explain the lack of detection of implicit memory.[6–8] For example, Standen and colleagues[8] exposed children to auditory stimuli during surgery before testing postoperatively with a cued recall technique (such as the category generation). However, it has been suggested that only one form of implicit memory, perceptual implicit memory, persists during adequate general anaesthesia in adults, and the use of a test involving conceptual processing may therefore be inadequate.[5] Other authors exposed anaesthetized children to the repeated auditory presentation of neutral phrases including a colour combined with an object (‘the child is playing with an orange/green ball’). Thereafter, a colouring task was used in the postoperative period to detect preferences for the colours presented during the previous general anaesthesia (a picture with a child playing with a multifaceted ball was presented to the child, who had to choose a colour for each facet of the ball).[6 7] In this test, there was no physical match between the stimuli presented during the first and second phases of the test, which could have reduced the implicit memory effect. Indeed, perceptual implicit memory depends on the physical similarities of stimuli during the study and test phases. It has been reported that implicit memory is reduced or abolished when perceptual characteristics (i.e. the modality of presentation) are modified between the first and second phases of the test.[22]

Andrade and colleagues[10] recently utilized a perceptual implicit memory task that had previously been tested in a control group. Sixteen words were played 20 times during surgery. On recovery, the children attempted a word identification task which consisted in presenting the target words and the distractor words embedded in white noise. Despite the use of a sensitive and pure perceptual implicit memory test, no evidence of implicit memory during general anaesthesia could be demonstrated in children aged between 5 and 18 yr. In brief, in the present state of our knowledge, the results of the study by Andrade and colleagues[10] raised the question of whether children cannot really develop memory representation during general anaesthesia unlike adults, or whether it follows from the procedural characteristics of the memory tests used so far in children.

In order to investigate the role of the type of test in the detection of implicit memory in children undergoing general anaesthesia, we used a perceptual implicit memory task that ensures various advantages. In fact, it is based on the mere exposure effect, which is an implicit manifestation, independent of explicit memory.[19] Indeed, a number of neuropsychological studies have demonstrated a normal mere exposure effect in amnesic patients, despite a profound inability to recognize the exposed stimuli.[17 18] Furthermore, it has been demonstrated that explicit recognition does not improve the mere exposure effect. On the contrary, the explicit recognition reduced this implicit memory effect.[15 23] For example, a meta-analysis indicated that stimuli perceived without awareness produce substantially larger mere exposure effect than do stimuli that are consciously perceived and thus recognized.[15] These findings offer a strong argument for postulating that the mere exposure effect is an implicit memory manifestation, independent of explicit memory.[19]

Additionally, in the present study, the quality of the pronunciation of the words was deteriorated by means of a low-pass filter, in order to reduce the conceptual component of the information and to preserve its perceptual aspect. In this way, the probability that the subject consciously made a link between the two phases of the test, and thus used an intentional retrieval strategy, was reduced. A time constraint was also used in order to minimize possible contamination by explicit memory. Another important aspect of our test is that it did not imply a high level of language capacity to respond, which was perfectly adapted for children. Despite the use of this test based on such a robust phenomenon, which has been demonstrated to be reliable in a control group, we failed to demonstrate any implicit memory in children undergoing general anaesthesia.

Finally, it must be emphasized that conflicting results were reported in adults after the application of a test exploring the mere exposure effect. Block and colleagues[24] showed that implicit memory persists during general anaesthesia, whereas other authors[25–27] failed to demonstrate the maintenance of implicit memory. However, these conflicting results may be attributed to the lack of standardization of the anaesthetic regimen, to the methodological design of the studies, or to both (i.e. the timing and the number of presentations of the stimuli, and the delay between the two phases of the implicit memory test differed between the studies). Accordingly, variable melodies or nonsense words[27] repeated at different times were presented to patients after the anaesthesia induction[27] or the surgical incision,[25 26] whereas memory testing took place at different times after surgery in all studies.[25–27] Moreover, the anaesthetic regimen differed in all studies, and, despite the use of total i.v. anaesthesia or inhalation anaesthesia, all studies failed to demonstrate the maintenance of implicit memory.[25–27] The only positive study that has been reported in adults after the use of a test based on the mere exposure procedure involved a different methodological design: nonsense words were presented two, four, eight, or 16 times during general anaesthesia, 5 min after the surgical incision, and were tested on the day after the operation. The results revealed that the patients preferred the nonsense words that were presented 16 times to those presented less often. The type of anaesthesia (nitrous oxide plus opioids, or nitrous oxide with isoflurane) did not affect implicit memory.[24]

In contrast to the study of Block and colleagues,[24] the number of presentations of the stimuli was smaller in the present study, which could have reduced the mere exposure effect. These explanations should be considered with caution, as tasks based on the mere exposure procedure have rarely been used. The results so far do not allow any conclusion as to the sensitivity of the mere exposure procedure in detecting implicit memory during anaesthesia in children. Further investigations should be undertaken in order to determine whether perceptual implicit memory tasks are adversely affected by anaesthesia in children. For instance, a word stem completion task could be used as in adults' studies in which perceptual implicit memory was demonstrated.

Although the depth of anaesthesia may explain the persistence or not of implicit memory during general anaesthesia, the effect of the anaesthetic regimen is less clear. Implicit memory has been shown to be present in adults when stem completion tasks with different anaesthetic regimens are applied,[4 28] suggesting that implicit memory is a general feature of anaesthesia. Similarly as in the study by Andrade and colleagues,[10] anaesthesia was maintained in our study with isoflurane, but both studies failed to report the presence of implicit memory. Nevertheless, this regimen has been shown to maintain a perceptual implicit memory effect in adults.[4] The maintenance of implicit memory has also been demonstrated during propofol anaesthesia in adults.[28] Hence, the anaesthetic regimen in adults does not seem to affect implicit memory under anaesthesia. Because neurodevelopment lasts for many years in children, and because the effects of hypnotic drugs may be different under such conditions, the potential effects of anaesthetic agents on implicit memory in children cannot be extrapolated from the results obtained in adults.

In the present study, we used the routine anaesthetic regimen applied in our institution. Induction of anaesthesia was either by inhalation or i.v., and maintenance was standardized with isoflurane and fentanyl. Moreover, the implicit memory test was applied just after incision at a step where all children were under the same anaesthesia regimen and lasted for <5 min. Therefore, it is unlikely that the impact of induction may have played a role on the persistence or not of implicit memory.

The depth of anaesthesia may explain the possible blunting effect on the implicit memory. Accordingly, studies have demonstrated that implicit memory is a persistent phenomenon at an adequate level of anaesthesia (BIS 41–60), but not during a deeper level (BIS 21–40).[4] Similarly as in previous studies,[6–8] we did not control the level of anaesthesia in the present investigation. The absence of BIS may be considered a limitation of the present study. However, as our implicit memory test lasted <5 min, it is unlikely that the depth of anaesthesia may have played a role on the persistence or not of implicit memory.

In conclusion, no evidence of perceptual implicit memory could be demonstrated in children when a task based on the mere exposure procedure was utilized. This result might suggest that children cannot develop memory representation during general anaesthesia unlike adults. However, this interpretation should be considered with caution. Indeed, this finding may be also attributed to various factors, such as the task used (an insufficient number of presentations of the stimuli, the short duration of the task, or the relatively low sensitivity of the procedure to detect implicit memory during general anaesthesia in children), the small number of children in the present study, the depth of anaesthesia, and the effects of drugs on the children's brain. Further research involving a large number of presentations of the stimuli during general anaesthesia should be undertaken in a large cohort of children with control of the depth of anaesthesia in order to determine whether the mere exposure effect is a sensitive procedure in detecting implicit memory during general anaesthesia.

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