Age-dependent and age-independent human memory persistence is enhanced by delayed posttraining methylphenidate administration

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Healthy human volunteers 16–82 years of age with at least 10 years of schooling were exposed to two different memory tasks. The first task involved incidental memory. The subjects were asked, as casually as possible: ''Did you watch any movie on TV 2 days ago? And 7 days ago? If so, do you remember the title of the movie(s) and the name of the first two actors (actresses)?'' Retention scores (maximum = 3: title, actor 1, and actor 2) were equally high (overall mean = 2.6, $n = 61$) in all age groups (16–20, 21–30, 31–40, 41–60, and 61–82 years) for the day 2 scores. Scores for the movie seen 7 days before decreased significantly and progressively in the three older groups in relation to age, which indicates reduced persistence of this type of memory beginning at the age of 41–50 years and becoming more extensive over the years. The other task was a formal memory procedure. Subjects were asked to study a brief text with factual information on the 1954 World Soccer Cup for 10 min. They were then exposed to 10 questions on the text 2 days and, again, 7 days later. Retention scores declined between the two tests, but in this task, the decline of persistence occurred to a similar extent in all age groups, and thus was not dependent on age. Methylphenidate (10 mg p.o.) given 12 hours after acquisition markedly enhanced persistence of the two memory types. This suggests an involvement of dopaminergic processes in persistence in the late posttraining period.

aging | human aging | incidental memory | formal memory

According to most accounts (1–3), memories take several hours to consolidate. According to other accounts, consolidation goes on through months or years (4), or at least for many days (5, 6). Once consolidated, long-term memories may persist for hours, days, or years (1). Their persistence depends on several factors: the degree of emotional arousal at the time of consolidation (3, 7), age (8–11 years), perhaps circadian oscillations (6), and other factors (5). A specific BDNF-dependent mechanism for memory persistence has been described in the hippocampus of rats, which is activated around 12 hours after training (12, 13).

Memories acquired without formal training and/or expectation of a retention test are called incidental (9, 14–17). No doubt, a major part of regular declarative memories is incidental (18, 19); we just learn as we live. Incidental memories use prefrontal and medial temporal structures for encoding and retrieval as intentional memories do (17, 20, 21). It was acknowledged long ago that the intention to learn adds nothing by itself to whatever is learned (16). Thus, perhaps the distinction between incidental and formal learning is more in the minds of the investigator(s) than in those of the subjects being trained or tested. All one-trial learning in humans or laboratory animals is, of course, incidental: it is acquired and retrieved unwittingly.

Here, we study the persistence of two different memories in humans aged 16 to 82 years. One consisted of remembering whether the subjects had watched a movie on television 2 or 7 days before. The other consisted of remembering data acquired by studying a brief text 2 or 7 days before. The former can be called incidental, and the latter was formally acquired and retrieved (16, 22). As will be seen, persistence was dependent on age in the former but not in the latter. In both cases, however, it was markedly enhanced by methylphenidate given p.o. approximately 12 hours after acquisition. As commented in *Materials and Methods*, methylphenidate is a drug widely used for the treatment of attention-deficit disorder and is widely believed to act through enhancement of dopaminergic synapses.

Results

In total, 105 normal healthy volunteers, 50 men and 55 women, aged 16–82 years with at least 10 years of schooling were studied.

Incidental Memory Task (Movies). Seventy-nine of the subjects were exposed to the incidental memory test. We simply asked them, as casually as possible, whether they had watched a movie on television 2 days or 7 days before, and if they had, whether they remembered the name of the movie and that of the two main actors or actresses. The subjects had not been instructed to watch the movies; they did so of their own will. The veracity of the subjects' reports was ascertained in 30 cases by asking somebody else in their household whether they had effectively seen that movie. The remaining participants lived alone or we had no direct access to others in their households, so we had to rely on their own word for it. Each correct response (name of movie and names of 2 actors) was awarded 1 point; thus, the maximum score was 3 for the 2-day or 7-day interval.

Fifty-five of the subjects reported having watched television movies 2 and 7 days before; the other 24 reported having seen a movie 2 or 7 days before. No significant differences in scoring at the 2-day or 7-day interval were detected between the two groups ($P > 0.2$; data not shown).

When the population was subdivided into age groups (16–30, 31–40, 41–50, 51–60, and 61 or more years of age), no significant differences in scores between groups for the 2-day interval were seen in one-way ANOVA [$F\ (4, 61) = 4.22$, $P > 0.1$] but there were large and significant differences between groups for the 7-day scores [$F\ (4, 65) = 18.88$, $P < 0.01$] (Table 1). These were significantly lower in the three older groups than in the two younger ones; furthermore, they were lower in the 51- to 60-year-old age group and the greater than 61 year-old age group than in the 41- to 50-year-old age group in the results of Duncan multiple-range tests at a level of $P = 0.001$.

Thus, memory persistence declined with age in this task, and this was already detectable at the age of 41–50 years. No internal correlations between age and memory scores were detectable within this age group ($r = 0.12$ and 0.14 for 2-day and 7-day scores, respectively; $n = 12$; $P > 0.1$).

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Table 1. Retention scores in the movies task in different age groups

Age group	2 days$^{(n)}$	7 days$^{(n)}$
16–30 years	2.9 ± 0.1$^{(17)}$	2.9 ± 0.1$^{(16)}$
31–40 years	2.7 ± 0.1$^{(10)}$	2.3 ± 0.3$^{(12)}$
41–50 years	2.5 ± 0.3$^{(10)}$	*1.9 ± 0.1$^{(12)}$
51–60 years	2.8 + 0.2$^{(8)}$	†‡0.9 + 0.4$^{(10)}$
61 years or more	2.4 ± 0.1$^{(21)}$	†‡0.4 ± 0.2$^{(22)}$

*Different from 16–30 years group at $P < 0.02$.
†Same at $P < 0.01$.
‡Different from 7 days score of preceding group at $P < 0.02$.

Twelve of the subjects (7 men and 5 women aged 40–74 years) who were regular television movie viewers were found to have been taking prescribed methylphenidate on and off in the past year. These subjects were re-examined in the movies task. They were asked to take methylphenidate (10 mg) or placebo (children's aspirin) at 9:00 to 10:00 a.m. on consecutive days, and 7–8 days after the second pill, they were inquired about the movies seen on three consecutive nights: the one before and the one after each treatment. One subject failed to report on the movie seen the night before the drug, and another subject failed to report on the movie seen the night before the placebo. Because each subject was examined about the movies he or she had seen on consecutive nights (the one before each treatment and the one after the second treatment), there were a total of 34 observations (12 for each treatment condition). This permitted us to evaluate the effect of the drug and the placebo 10–13 hours after and 10–13 hours before the movies. Data were obtained in a double-blind fashion: neither the subjects nor the investigators knew beforehand which pill the subjects had taken. The methylphenidate and the aspirin pills were both white and of the same size.

Table 2 shows that methylphenidate given the morning after having watched the television movies markedly enhanced retention scores for the movie seen 7 days before relative to placebo [F (2, 31) = 25.58; $P < 0.01$; differences between postmethylphenidate and premethylphenidate or postplacebo were significant in Duncan multiple-range tests at level of $P < 0.001$). Therefore, methylphenidate reversed the decline of persistence seen with age. Performance at 7 days was as good in the methylphenidate group as it was in the 2-day test in any age group (Table 1).

Formal Memory Task (World Soccer Cup). The formal memory task involved asking the subjects to study a 15-line text with factual information on the 1954 World Cup of Soccer (see *Materials and Methods*) for 10 min and then to respond to a questionnaire 2 or 7 days later on 10 of the factual items of the text (22). Forty-two subjects (23 men and 19 women aged 16–78 years) were examined in this task, 25 of whom had participated in the movies task 2 or more weeks earlier.

Table 2. Retention scores in the movies task in subjects treated with placebo (children's aspirin) or methylphenidate (10 mg) p.o. 12 hours before or 12 hours after having watched a movie 7 days before testing

Treatment$^{(\text{hours from training})}$	Score$^{(n)}$
Placebo$^{(+12)}$	0.7 ± 0.3$^{(11)}$
Placebo$^{(-12)}$	0.6 ± 0.3$^{(5)}$
MPH$^{(+12)}$	*2.9 ± 0.1$^{(10)}$
MPH$^{(-12)}$	0.6 ± 0.3$^{(6)}$

MPH, methylphenidate.
*Different from all other groups at $P < 0.02$.

Table 3. Retention scores in the World Cup of Soccer tests carried out 2 and again 7 days after having studied the text

Age group	2 days$^{(n)}$	7 days$^{(n)}$
16–40 years	7.3 ± 0.3$^{(17)}$	*3.3 ± 0.5$^{(17)}$
41–60 years	6.7 ± 0.3$^{(13)}$	*2.8 ± 0.5$^{(13)}$
61 years or more	7.4 ± 0.4$^{(12)}$	*2.9 ± 0.2$^{(12)}$

*Different from 2 days score of same group at $P < 0.01$.

Findings are shown in Tables 3 and 4. In Table 3, it can be seen that there was low memory persistence of the 1954 World Cup information in all age groups: the difference between day 2 and day 7 scores was significant at level of $P < 0.001$ in individual Student t tests carried out in each age group (16–40, 41–60, or 61 or more years of age) and in a Duncan multiple-range test carried out following one-way ANOVA in all groups [F (5, 78) = 11.88, $P < 0.01$].

The 12 subjects who had participated in the pharmacological study reported in Table 2, plus 8 others who had also used methylphenidate on and off during the past year, were exposed to the Soccer Cup text at least 2 weeks after the movies test and then to the corresponding questionnaire 2 and 7 days after that. These 20 subjects (in total, 11 men and 9 women aged 35–74 years) were asked to take methylphenidate (10 mg) or placebo as discussed previously 10–12 hours after studying the text. The experiment was run double-blind. As seen in Table 4, methylphenidate markedly reduced the decline of memory persistence seen between days 2 and 7 ($P < 0.001$ in a Student t test). Actually, in the subjects who had ingested methylphenidate after studying the text, performance in the questionnaire was as good as it was in all subjects on day 2.

No gender differences were observed in the two tasks in the 2-day or 7-day scores in each age group or in the entire population of subjects (not shown).

Discussion

The most salient findings of this study are as follows: (*i*) memory can be made more persistent (i.e., to last 7 days instead of 2) by treatments given 12 hours after training in two different forms of memory in humans, as has been shown to be the case in rats for aversive learning (12, 13); (*ii*) methylphenidate, a dopaminergic drug widely used for the treatment of attention-deficit disorder (24, 27), can increase the persistence of age-dependent incidental memory and the formal memory of facts contained in a text; and (*iii*) persistence of the incidental memory studied declined with age, and the effect of methylphenidate taken 12 hours after acquisition was seen in subjects of all ages.

It is perhaps not surprising that persistence of the incidental memory studied declines with age. This was shown years ago for other incidental learning (9, 15). The one-trial memory task, whose persistence declines with age in rodents (8, 9), is, of course, also incidental, as are all laboratory training and testing in this kind of task.

Table 4. Retention scores in the World Cup of Soccer tests carried out 2 and again 7 days after having studied the text in subjects who received placebo or methylphenidate (10 mg) 12 h after studying the text

Treatment	2 days$^{(n)}$	7 days$^{(n)}$
Placebo	7.1 ± 0.2$^{(10)}$	*2.9 ± 0.2$^{(10)}$
MPH	7.3 ± 0.2$^{(10)}$	*7.9 ± 0.2$^{(10)}$

MPH, methylphenidate.
*Different from all other groups at $P < 0.01$.

Incidental memory is highly relevant to orientation in time (15, 16) and to the performance of activities that people older than 40 or 50 years of age tend to regard as difficult because of constantly changing rules or an excess of information (e.g., driving in the city, using new computer programs). Actually, it is likely that most memories in humans are incidental, because they are acquired through daily experience and, most often, without the subjects actually setting out to make them or evoke them; this certainly applies to most memories made in classrooms or other formal settings.

The present results indicate that decreased persistence of incidental memory begins at the age of 41–50 years (i.e., much earlier than most subjects can be regarded as being truly aged). In rats, the decline of memory persistence also begins when they approach middle age (1 year; refs. 8, 9, 23). It has been known for a long time that mnemonic and anatomical signs of decline appear in the human brain decades before senescence and progressively increase with age, starting as early as the age of 40 years or so (9, 15).

There was no inkling of age-dependent persistence loss in the text-questionnaire task. Persistence declined in all age groups. This might be attributable to the perception by the subjects that the material they had to learn was not really important (22). Actually, when asked about it, all 12 subjects who participated in the pharmacological experiments of the two tasks said they thought that the movies were ''more important'' than the World Cup text. Thus, the low persistence seen in all subjects in this task may be attributed to a relative lack of attention or interest at the time the information was learned.

It must be noted that there was a procedural difference in the text-questionnaire task and the movies task. In the former, all subjects were exposed to the test questions twice, at 2 days and then again at 7 days after the original learning. In the movies task, the movies seen at the two test intervals were different, the questions about them were nearly always posed simultaneously, and, of course, the answers to one were irrelevant to the answers on the other one. Clearly, in the World Soccer Cup, the test at 2 days after training did not serve as a reminder for the 7-day test or a reconsolidation test. There is no apparent reason why it would have served an extinction purpose either.

The results are compatible with a role of the recently described hippocampal mechanism of memory persistence for one-trial avoidance and contextual fear conditioning in rats (12, 13). Methylphenidate stimulates dopamine release in the forebrain by influences on the dopamine vesicular transporter (24–27), and it was reported long ago to enhance learned behaviors in rats (28, 29) and, more recently, in humans (30). The hippocampus detects novelty (31, 32) and plays a key role in memory consolidation (2), which relies on novelty (33). Lisman and Grace (34) proposed that the detection of new information by the hippocampus is relayed to the ventral tegmental area (VTA) through the subiculum, accumbens, and ventral pallidum and that the VTA, in turn, projects to the hippocampus through dopaminergic fibers acting on D_1 receptors, where it enhances long-term potentiation (LTP) and learning. The hippocampal-VTA loop has, in fact, been found to be important for novelty detection (32), for the generation and maintenance of hippocampal LTP (35), and for memory consolidation (34, 36). The VTA plays a key role in psychomotor stimulation, particularly in the generation of drug addiction, mediated by local glutamate receptors and dopamine projections to the accumbens and elsewhere (37–40). It was recently found that a single dose of cocaine can induce glutamate receptor-mediated LTP in the VTA (41, 42), which should, of course, keep dopamine release enhanced at VTA projection sites for many hours, perhaps but not necessarily in spurts (e.g., ref. 6). A mechanism of this sort could, of course, explain several aspects of the long-lasting behavioral changes that are initiated by VTA activation, such as drug addiction (43) and memory persistence (12, 13). Methylphenidate could well be acting on memory persistence by fostering such a mechanism.

The findings with methylphenidate do not necessarily suggest that the low persistence seen in either of the two tasks must be treated. It is certainly possible that it represents a physiological process by which relatively irrelevant or unimportant information is forgotten, whatever the word ''forgotten'' is taken to mean (i.e., memory loss, low availability for retrieval).

Materials and Methods

The 105 subjects studied were residents of Brazil and Argentina. Approval was obtained from the Ethics Committee for Research of the Binational Brazil-Argentina Panel for Science, in agreement with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants had been found to be normal from a neurological and psychiatric viewpoint in routine examinations carried out at their schools and/or working places.

Two memory studies were carried out: 77 subjects were exposed to an incidental memory study and 41 to a formal memory task (22). Twelve of the latter had been previously exposed to the other memory test. The text used for acquisition of the formal memory task, translated into English, was as follows: ''The 1954 World Cup of Soccer was played in Switzerland. The 16 teams were divided into four groups for the qualifying round. Brazil defeated Mexico (5 to 0), tied with Yugoslavia (1 to 1), and conquered group 1. Hungary trounced Korea (9 to 0) and West Germany (8 to 3) and won group 2. Germany had to defeat Turkey twice, 4 to 1 and 7 to 2, to come in second in that group. Hungary eliminated Brazil 4 to 2 in the quarterfinals, in a match plagued by violence in which three Brazilians were sent off. Also in the quarterfinals, Germany defeated Yugoslavia 2 to 0 and Uruguay defeated England 3 to 1 in a dramatic game in which Uruguay's legendary captain Obdulio Varela scored, suffered a fracture, and went on playing with a broken leg for several minutes. In the semifinals, Germany eliminated Austria 6 to 1 and Hungary defeated Uruguay 4 to 2. Austria then beat Uruguay for third place. The final game was intense. Hungary got off to a 2 to 0 start, but Germany turned the game around 2 to 2 with a goal by Rahn with 6 min to go, and thus won its first cup.''

The questionnaire consisted of the following questions. ''Who won group 1?'' ''Who won group 2?'' ''How many times did Germany play against Turkey?'' ''Who obtained third place?'' ''How many times did Germany and Austria play against each other?'' ''What were the scores of the two Hungary vs. Germany games (a choice among 4 possibilities)?'' ''Was the Hungary vs. Brazil match normal?'' ''What happened to Uruguay's captain in the game against England?'' ''What team scored first in the final game?'' ''What player scored the last goal of the Cup?'' Each question was awarded 1 point.

Written consent was required for participation in the pharmacological studies. As mentioned previously, all subjects in this group had previous experience with prescribed methylphenidate in the preceding year.

Results were analyzed by Pearson *r* correlations and one-way ANOVA, followed by Duncan multiple-range tests and/or Student *t* tests when applicable.

Methylphenidate was introduced into medical practice a quarter of a century ago (24–30). It is widely used for the treatment of attention-deficit disorder in children and adults [and is widely believed to exert its central effects by stimulating dopamine release in the forebrain (24–27)].

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