

Time-Dependent Motor Memory Processes in Amnesic Subjects

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Shadmehr, Reza, Jason Brandt, and Suzanne Corkin. Time-dependent motor memory processes in amnesic subjects. *J. Neurophysiol.* 80: 1590–1597, 1998. Functional properties of motor memory change with the passage of time. The time-dependent nature of memories in humans has also been demonstrated for certain “declarative” memories. When the declarative memory system is damaged, are the time-dependent properties associated with motor memories intact? To approach this question, we examined five subjects with global amnesia (AMN), including *subject H.M.*, and a group of age-matched control subjects. The task was to make reaching movements to visually presented targets. We found that *H.M.* (but not the other subjects) was significantly impaired in the ability to perform the visuomotor kinematic transformations required in this task, to accurately move the hand in the direction specified by a target. With extensive practice, *H.M.*'s performance improved significantly. At this point, a force field was imposed on the hand. With practice in field A, *H.M.* and other AMN subjects developed aftereffects and maintained these aftereffects for 24 h. To quantify postpractice properties associated with motor memories, subjects learned field B on day 2 and at 5 min were retested in field A. In both subject groups, performance in field A was significantly worse than their own naive performance a day earlier. The aftereffects indicated persistence of the just-learned but now inappropriate motor memory. After 4 h of rest, subjects were retested in B. Performance was now at naive levels. The aftereffects at 4 h indicated a reduced influence of the memory of field A. The time-dependent patterns of motor memory perseveration, as measured at 5 min and 4 h, were not different in the AMN and normal control groups.

INTRODUCTION

Recent experiments suggested that learning a perceptual or a visuomotor skill initiates memory processes that continue to develop long after termination of the practice session. This view was inferred from four observations. First, soon after learning a visuomotor association requiring arm movements, learning a reversed (Lewis et al. 1949, 1951a,b) or anticorrelated (Shadmehr et al. 1995) version of the association is significantly inhibited compared with the performance of naive subjects. With an increasing temporal distance between learning of the first and second tasks, learning rates in the second task improve significantly (Bunch 1939; Flook and McGonigle 1977; Shadmehr and Brashers-Krug 1997). Therefore it seems that learning a visuomotor association initiates a strong anterograde functional process that declines with time. Second, in learning a perceptual skill,

disruption of sleep soon after acquisition of the skill diminishes recall (Karni et al. 1994). Soon after acquiring a motor skill, learning of an anticorrelated skill also diminishes recall (Brashers-Krug et al. 1996; Rey-Hipolito et al. 1997). With the passage of time, sleep disruption and learning of the second task have a reduced effect on recall. Therefore the influence of certain postpractice events, i.e., retrograde interference, is strongest when the temporal distance between the event and the instance of learning is short. Third, in some motor and perceptual tasks, subjects improve rapidly during the practice period and then show further, slower improvement in performance without further practice during the hours (Jackson et al. 1997) and days that follow (Karni et al. 1994). Fourth, functional imaging provides evidence that some of the time-dependent behavioral phenomenon may be correlated with time-dependent shifts in activation patterns in the brain (Shadmehr and Holcomb 1997).

Time-dependent gradients of retrograde and anterograde interference are not limited to motor tasks. They have also been observed when subjects learn certain “declarative” information. For example, time-dependent gradients of retrograde and anterograde interference were observed when subjects learn to associate word A with word B, followed by learning the pairing of the same word A with new word C (Koppelaar 1963; Postman et al. 1968; Underwood 1948). Because learning of a novel motor skill also involves acquisition of declarative information about the task, it is possible that the interference observed in learning of motor skills is actually a result of the declarative components inevitably present. To test this possibility, we examined motor learning in a group of individuals with severe impairment in their declarative memory system, i.e., amnesic (AMN) patients. It is known that AMN patients can learn and retain some motor skills [e.g., mirror tracing (Gabrieli et al. 1993; Milner 1962), rotary pursuit (Bondi et al. 1993; Corkin 1968; Tranel et al. 1994; Yamashita 1993), and bimanual tracking (Corkin 1968)], despite the fact that they may not be able to recall the training episodes. However, interference properties associated with motor memories were not examined in the AMN population. If acquisition of motor memory initiates a postpractice pattern of interference that is independent of the declarative memory retained from the task, then one would predict no difference in the behavioral consequences of learning multiple motor skills in severely AMN and normal subjects. Here we initially asked whether learning and retention of a task that involved reaching to targets in a force field was normal in an AMN population. We then measured interference during sessions in which the force field was reversed.

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METHODS

We compared motor learning in a group of nondemented global AMN subjects ($n = 5$) with that of normal control subjects (NCSs) ($n = 5$). The groups did not differ significantly in age or educational levels. The first AMN subject was *H.M.*, age 69 at the time of testing. *H.M.* underwent bilateral medial temporal lobe resection in 1953. A recent magnetic resonance imaging (MRI) (Corkin et al. 1997) indicated that the surgeon removed bilaterally the medial temporal polar cortex, most of the amygdaloid complex, and all of the entorhinal cortex. In addition, the anterior portions of the dentate gyrus, hippocampus, and subicular complex were removed. The ventral perirhinal cortex and the posterior parahippocampal, lingual and fusiform gyri are intact. Outside *H.M.*'s temporal lobe, there is marked atrophy of the cerebellar vermis and hemispheres, but frontal, parietal, and occipital lobe cortices appear normal. *H.M.* also has peripheral neuropathy in his hands and forearms with reduced somatosensory function, including pressure sensitivity, two-point discrimination, point localization, and position sense (Hebben et al. 1985). The second AMN subject, *J.R.*, was a 61-yr-old woman whose AMN followed herpes simplex encephalitis. Her MRI indicated increased signal intensities, consistent with inflammatory processes, bilaterally in the parahippocampal gyrus (Benedict et al. 1993). The remaining AMN patients were a 77-yr-old female, 62-yr-old male, and 46-yr-old male. The etiologies of their AMNs were unknown. Mean age and education for the AMN group were 64 ± 9 and 15 ± 2 (SD) yr, respectively. The NCS group consisted of three women and two men, ranging in age from 57 to 77 yr (mean of 65 ± 8), with a mean education of 14 ± 2.5 yr. All subjects, including *H.M.* (Corkin 1984), were right handed.

Subjects were studied over a 2-day period. They were seated in front of a robot manipulandum and instructed to grab its handle with their right hand. Subjects were instructed to make targeted reaching movements while holding the robot (Shadmehr and Brashers-Krug 1997). The goal was to reach a target (distance of 10 cm) within a time limit (feedback regarding timing provided after each movement). The timing goal for each subject was adjusted based on the peak tangential velocity observed in the movements to the first 100 targets. As noted before (Corkin 1968), *H.M.* moved significantly slower than NCSs. His goal was set at 1.2 s. The timing goal for the remaining group of AMN subjects was set at 0.7 ± 0.1 s and for the NCS group at 0.65 ± 0.1 s.

On day 1, session 1, subjects began by moving the robot in a null field, i.e., the robot motors turned off. After 384 targets (2 target sets, each set consisting of 192 targets), all subjects except *H.M.* were able to make straight, smooth movements. We provided *H.M.* with 384 extra targets; by the end of this training he was able to make fairly straight movements to the targets. At this point, robot motors were engaged, and a force field was produced. Subjects were told that the robot would now push their hands. Subjects were asked to move the handle (at their own pace and without any targets) and experience the forces for 10–15 s, after which we began targeted movements. The field was defined as a function of hand velocity and a curl viscous matrix (Shadmehr and Brashers-Krug 1997). It perturbed movements by producing forces that were perpendicular to the direction of motion. The curl matrix that defined the field was scaled based on the peak tangential hand velocity in the null field to compensate for the slower movements of the AMN group. The force field learned during session 1 of day 1 was labeled as field A. Training in this field continued for 480 targets. For randomly selected targets, the field was unexpectedly removed, resulting in aftereffects (Shadmehr and Mussa-Ivaldi 1994a). The frequency of the aftereffect was, on average, one in six targets. The size of the aftereffects at 250 ms into the movement was quantified as the amount of deviation (perpendicular distance) from a straight line path to the target. The size had a negative sign

if the aftereffect was a clockwise displacement from the straight line path and a positive value otherwise.

Session 2 of day 1 began 4 h after completion of session 1. We tested for retention of field A by having subjects make reaching movements to 192 targets in field A. Subjects then returned the next day. Session 1 of day 2 began with 100 targets in the null field. After a 2-min rest, 384 targets were presented in field B. This field was mathematically anticorrelated with field A, i.e., each force vector was rotated 180° . Five minutes after completion of practice in field B, subjects were given 380 targets in field A. Subjects then left the testing room and returned 4 h later. Session 2 of day 2 consisted of 192 targets in field B (except for *H.M.*, who was tested on only 77 targets). Throughout the sessions, we recorded hand position, velocity, and imposed force at 100 Hz.

RESULTS

Declarative memory impairment in AMN is typically assessed by recall of word lists and story passages and recognition and reproduction of spatial patterns. The Wechsler Memory Scale-Revised test (WMS-R) provides widely used indices of these skills, which are on the same scale as the intelligence quotient (I.Q.), with a mean of 100 and SD of 15. The degree to which the general memory index of the WMS-R (especially the delayed recall index) falls below the I.Q. provides a measure of the severity of the global AMN (Table 1). In a normal population, the WMS-R delayed recall index should be approximately the same as the I.Q. The intelligence of all AMN subjects was in the average to superior range, whereas their ability to recall recently acquired declarative material was significantly impaired.

The consequences of this memory impairment were particularly striking in subjects *H.M.* and *J.R.* At the start of session 1 on day 2, despite 3 h of training with the robot on the previous day, these subjects said that they never saw the robot before, and they could not begin to describe the task. Throughout the experimental sessions, *H.M.* mentioned that the task reminded him of a favorite pastime of his when he was younger, hunting for small game (the reason for this response perhaps was because when the hand reached the target in time the target “exploded”). He then described in detail the type of game that he hunted for and the guns that he used. Although we did not record the conversation, he repeated this description at ~ 10 -min intervals, each time with the same enthusiasm he expressed the first time.

In session 1 on day 1, subjects learned to move the robot in a null field and then were trained in a force field. The purpose of the null field training was to allow the subjects to learn the timing of the task and its kinematics, i.e., the spatial transformation from the plane of the monitor to the plane of the hand. *H.M.* had severe difficulties in learning the kinematics of the task. Initially, he was not able to move his hand accurately toward the target (Fig. 1A). During the first 100 movements, the absolute values of the directional error at 150 ms into the movement were $37 \pm 5^\circ$ (SE; Fig. 1B). After 600 movements, these errors were reduced to $19 \pm 2^\circ$ (a significant reduction, paired *t*-test, $P < 0.0005$), resulting in straighter movements to the targets (Fig. 1C). In comparison, the remaining AMN subjects started with directional errors of $13 \pm 4^\circ$ and after completion of training in the null field had average errors of $8 \pm 2^\circ$ (a significant reduction, paired *t*-test, $P < 0.05$). The NCS group showed

TABLE 1. Characteristics of amnesic subjects and their performance on tests of intelligence, attention, and memory

Subject	Sex	Age	Education	Full Scale I.Q.	WMS-R Attention	WMS-R General	WMS-R Delayed
<i>H.M.</i>	M	70	12	99	78	74	54
<i>J.R.</i>	F	61	16	111	111	89	54
<i>M.C.</i>	F	77	18	123	113	92	71
<i>R.J.</i>	M	62	14	112	122	87	64
<i>R.H.</i>	M	46	16	122	97	89	67

similar results, $12 \pm 3^\circ$ at the start of training and $8 \pm 2^\circ$ at the end (a significant reduction, paired *t*-test, $P < 0.05$). Because the spatial transformation was similar to that required to use a computer's mouse, we selected a majority (3/5) of our control subjects (aged 56-, 62-, and 77-yr old) such that they had no previous experience with computers. Among this subgroup of NCS, initial directional errors were $13 \pm 1^\circ$, significantly less than those observed in *H.M.* Despite this handicap, *H.M.* improved markedly with practice in the null field and when tested on day 2 displayed retention; directional errors and movement lengths were significantly

less during retesting on day 2 compared with naive performance on day 1 (comparison of 1st 100 movements on day 1 with day 2, paired *t*-test, $P < 0.0005$ for movement direction, $P < 0.001$ for movement length). Lengths and directional errors were not significantly different for any group during retesting on day 2 compared with that group's trained performance on day 1. Movement length and directional errors of *H.M.* on day 2 were not significantly different from other AMN subjects or from the NCS group. Therefore *H.M.*'s ability to perform the kinematic transformation required in this task was significantly impaired. With extensive training, his performance improved significantly and was maintained over a 24-h period.

We next examined the ability of *H.M.* and other subjects to learn the dynamics of a novel mechanical system. After practice in the null field, the robot motors were engaged and subjects had to make reaching movements in field A. As previously noted (Shadmehr and Mussa-Ivaldi 1994a), the field significantly perturbed hand trajectories (Fig. 2A), resulting in increased movement length. The changes in movement length from null to initial performance in the field (cf. Fig. 1C with Fig. 2C) were not significantly different among *H.M.*, other AMN subjects, and the control group, suggesting that the field perturbed movements by approximately the same amount (with respect to the null field) in all subjects. With practice, movement length decreased significantly in both groups (comparison of the last 100 movements with the 1st 100, paired *t*-test, $P < 0.02$ for each of the groups), indicating adaptation.

We expected that learning of an internal model would result in improved ability of the motor system to predict behavior of the force field and to compensate. As a consequence, if the field were removed unexpectedly, then there should be aftereffects. We found aftereffects in all subjects. Figure 2, A and B, illustrates, respectively, the hand trajectory of *H.M.* during the initial stage of training in the field and his aftereffects near completion of practice in session 1 of day 1. The size of the aftereffects, measured as the distance from a straight line trajectory to the target at 250 ms into the movement, increased in all subjects as they practiced movements in the field (Fig. 2D, comparison of the last 16 aftereffects in the force field with those recorded in the null field before exposure to the field, $P < 0.01$ for each groups). The progression was consistent with the gradual formation of an internal model. The aftereffects in *H.M.*, however, were significantly smaller than in those the other AMN subjects and in the NCS group. This result is likely caused by *H.M.*'s significantly slower movements; tangential velocity at 250 ms into the movements was 0.11 m/s for *H.M.* but 0.25 m/s for the remaining AMN group and 0.27 m/s for

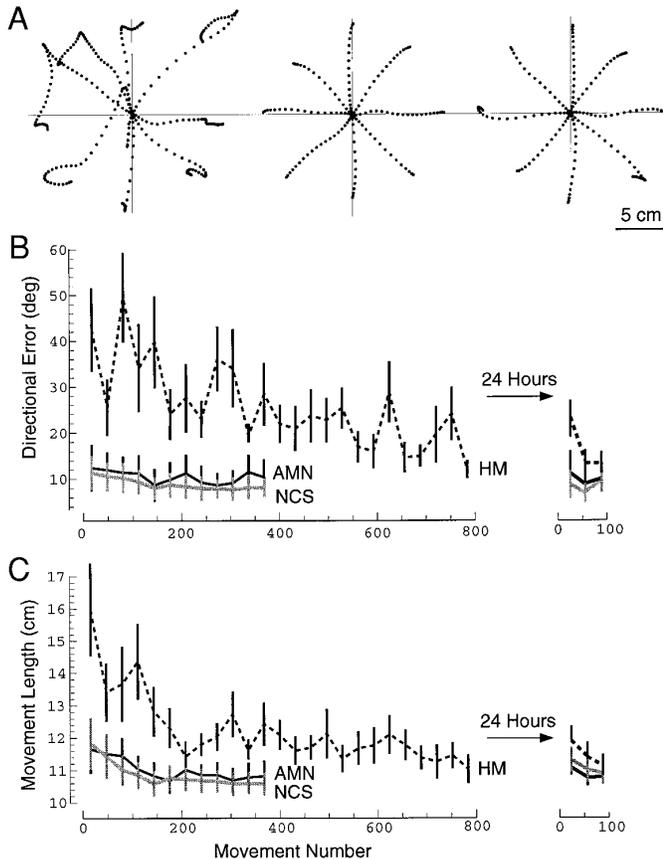


FIG. 1. Performance of *H.M.*, other amnesic (AMN) subjects ($n = 4$), and normal control subjects [normal control subjects (NCS), $n = 5$] in learning kinematics of the task in the null field. A: *H.M.*'s typical hand trajectories (points are 50 ms apart) during initial stages of practice in the null field (left), after 700 movements (middle), and during a test of recall 24 h later (right). B: absolute value of the error in the direction of motion (compared with the direction of target) at 150 ms into movement during practice in session 1 of day 1 and 24 h later. C: length of movements during practice in session 1 of day 1 and 24 h later. Points are means \pm SE; bin size is 32.

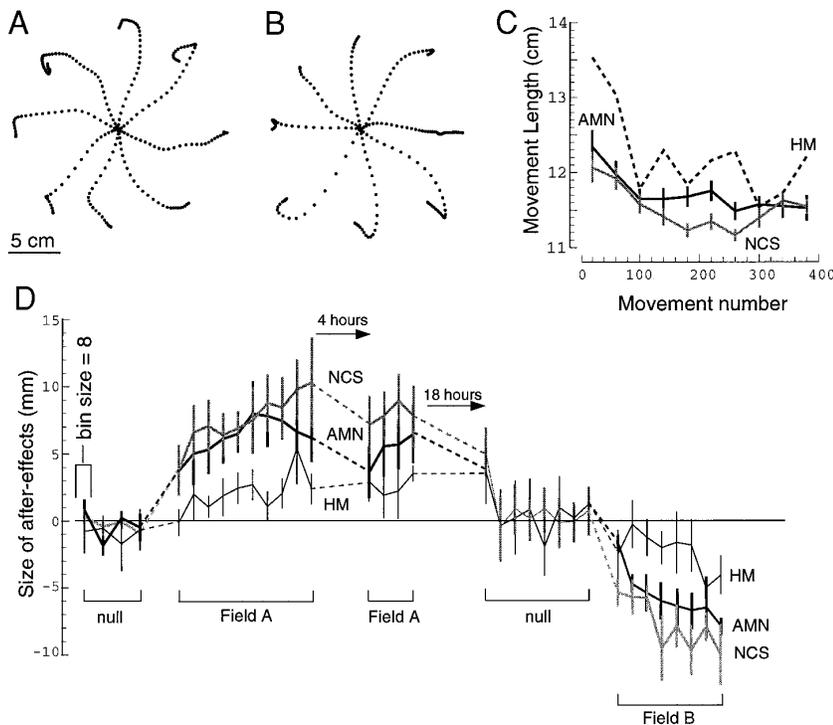


FIG. 2. Performance of *H.M.*, other AMN subjects, and NCSs during learning of arm movements in a force field. *A*: *H.M.*'s typical hand trajectories (points are 50 ms apart) during initial stage of practice in the force field. *B*: *H.M.*'s typical aftereffects after 300 movements in the field (points are 50 ms apart). *C*: length of movements during learning of the field. Points are means \pm SE. Bin size is 32. *D*: size of aftereffects was calculated at 250 ms into the movement and reflects a displacement from a straight line trajectory to the target. They are shown during null movements, during learning of field A, during recall of A at +4 h, during the null field on session 1 of day 2, and during learning of field B. Points are means \pm SE; bin size is 8. When there was a field present, an aftereffect occurred at random, but at approximately once every 6th target. Eighteen hours after completion of practice in the field, on day 2, aftereffects were still present but quickly dissipated as subjects practiced in the null field. On day 2, in the null field, the data for *H.M.* and the NCS group are plotted, but for the sake of clarity only the first and last data points for the AMN group are plotted. Values for this group during null field of day 2 were indistinguishable from the control group and *H.M.*

the control group. Because of this discrepancy, and despite our attempts to scale the force field, the forces experienced by *H.M.* were $\sim 40\%$ smaller than the remaining AMN group.

When subjects returned 4 h after initial exposure to field A, aftereffects were present (Fig. 2D). Further, the aftereffects were still present on day 2, despite the fact that 18 h passed since last exposure to the field (aftereffects on day 2 in the null field for the 1st 8 movements were significantly larger at $P < 0.01$ for each of the subject groups compared with those recorded in the last 8 movements in the null field on day 1). After a few movements in the null field on day 2, aftereffects disappeared. Taken together, *H.M.* and other AMN subjects learned the novel mechanical dynamics of reaching movements and exhibited long-term retention when tested on day 2.

H.M. retained many other components of this task. For example, in the target set, all odd-numbered targets were randomly selected, whereas the position of the even-numbered targets was always at the center. The center target was shown 1.0 s after completion of the even-numbered movement. To assess whether *H.M.* recalled this simple pattern, during session 2 of day 1, the first target was presented, but the presentation of the second target was delayed by 2.5 s. During this period, *H.M.* had no target to move to, yet after completion of the outward movement he went to the next target position at the center, although the target was not displayed yet. Two other observations are worth noting. On sitting in front of the robot on day 2, without prompting, *H.M.* reached for the sling that supported the arm, put his hand through it, and then grabbed the robot and looked up to the monitor. He kept on looking and moving the handle of the robot although the screen was blank. Naive subjects generally avoided the sling and did not touch the robot until they were shown how. Furthermore, naive subjects initially

concentrated on looking at their hand while they moved the robot rather than the monitor (which displayed motions on a plane perpendicular to that of the hand).

We next asked whether the interference that was reported in association with learning of this motor task was also present in the AMN population. On session 1 of day 2, subjects learned field B. Forces in field B were in an opposite direction to that of field A. In all subjects, the direction of the aftereffects reversed compared with those recorded on day 1 (Fig. 2D). After 5 min of rest, subjects were presented with field A. We then checked for retention of field B 4 h later. Field A was the same field that was learned on day 1.

To quantify interference, we examined the behavior of the arm early in the movement when the influence of the internal model was most observable (Wolpert et al. 1995). We quantified the degree of adaptation of the internal model by measuring how well the subjects were able to compensate for the field. The measure was the hand's displacement from a straight line path to the target at 250 ms. We asked whether learning of field B on day 2 affected recall of field A. This measure is an index of anterograde interference. Fig. 3A shows the performance of subjects in learning field A when they were naive (on session 1 of day 1) and when they were tested for recall (on session 2 of day 1). When subjects were naive, the field perturbed the arm, but with practice the magnitude of perturbation declined. When tested at +4 h, the learned behavior was sustained. However, when they were again tested for recall of A right after having learned field B (on session 1 of day 2), their performance was significantly worse than their performance as naive subjects; for *H.M.*, t -test of the displacements measured in the naive versus recall A (after B) target sets (100 targets), $\Delta = -0.14$ cm (average change over $n = 100$ targets), $P < 0.04$; for AMN (not including *H.M.*), paired t -test for the mean value of the displacements measured in the naive and recall

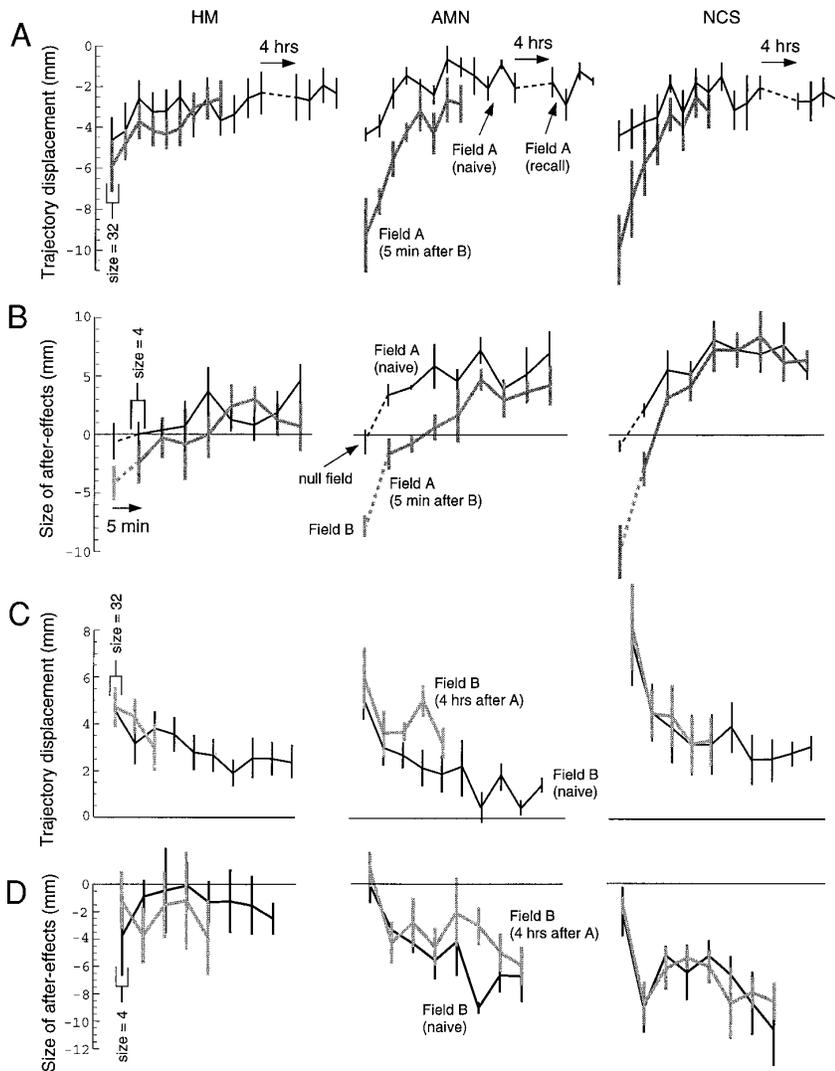


FIG. 3. Interference associated with motor memories in *H.M.*, other AMN subjects, and NCSs. *A*: displacement of the hand's trajectory from a straight line at 250 ms into the movement. *Dark lines*: initial learning of field A (session 1, day 1) and recall at +4 h (session 2, day 1). *Shaded lines*: relearning/recall of field A at 5 min after learning of field B (session 1, day 2). Points are means \pm SE; bin size is 32. *B*: aftereffects during learning of field A on day 1 (naïve condition, black lines) and relearning/recall on day 2 (5 min after B, shaded lines). Also shown are the aftereffects in the conditions immediately preceding performances in *A*. *C*: performance during initial learning of field B and during relearning/recall 4 h after performance in field A. *D*: aftereffects during initial learning of field B and during recall at 4 h.

A (after B) target sets in each subject, $\Delta = -0.391 \pm 0.15$ (SE) cm ($n = 100$ targets), $P < 0.05$; for NCS, paired t -test for the mean value of the displacements measured in the naive and recall *A* (after B) target sets in each subject, $\Delta = -0.358 \pm 0.09$ (SE) cm ($n = 100$ targets), $P < 0.01$. To our knowledge, this report is the first instance where anterograde interference was reported during learning of a visuomotor task in an AMN population.

The amount of interference, as measured by trajectory displacement, was smaller in *H.M.* compared with the rest of the AMN and NCS populations. This value, however, was within 1 SD of the interference observed in the AMN population and within 1.2 SD of the value observed in the NCS population (mean change in performance for 100 targets). Therefore based on this measure, there was significant anterograde interference in all groups, but the amount of this interference did not differentiate the groups.

Why is performance in field *A* (after B) significantly worse than naive? In a previous report, we found that acquiring a motor memory resulted in a pattern of perseveration that influenced future learning (Shadmehr and Brashers-Krug 1997). This bias was evidenced by the aftereffects

that subjects had as they started learning the second field. Similarly, in our current experiment, the aftereffects of B were present when subjects were attempting to recall A, as shown in Fig. 3*B*. Here the aftereffects during the naive *A* and recall *A* (after B) conditions are plotted for the first 200 movements in the field (note that on average every 6th target was in a null field, resulting in an aftereffect). When *A* was presented after B, the aftereffects suggested that subjects were attempting to relearn/recall A with the internal model appropriate for B. It is likely that this perseveration of the memory of field B was the reason for the worse-than-naive performance observed in Fig. 3*A*. In *H.M.*, the aftereffects were smaller. Nevertheless, over the first 100 targets the aftereffects were significantly biased compared with his naive performance (paired t -test, $P < 0.05$).

We further quantified the degree of this anterograde interference by comparing the aftereffects that subjects had during recall of *A* (after B) versus naive *A* conditions. Over the first 100 targets, corresponding to 16 aftereffects, the change in aftereffect size was -0.230 ± 0.123 (SE) cm for the NCS group, -0.176 cm for *H.M.*, and -0.455 ± 0.032 cm for the remaining AMN subjects. With the use of this

measure, we again found no statistically significant difference between the AMN and normal populations (*t*-test, $P > 0.2$).

Four hours after learning fields B and A in sequence, subjects were again presented with field B. Because 4 h passed since subjects were exposed to field A, we expected that they would show significantly smaller amounts of perseveration than that observed at 5 min. We found that performance during the recall test for B was at naive levels (Fig. 3C) and not worse than naive, as seen during recall of A during session 1 of day 2. The AMN subjects, including *H.M.*, performed at a level that did not differ significantly from their naive performance ($\Delta = +0.095 \pm 0.04$ cm, $n = 100$ targets, 77 for *H.M.*, paired *t*-test, $P = 0.065$). In the NCS group, performance in B during recall was also at naive levels ($\Delta = +0.041 \pm 0.044$ cm, $n = 100$ targets, paired *t*-test, $P = 0.23$). The magnitude of aftereffects during naive B and recall of B conditions are shown in Fig. 3D. The recall began with essentially a naive internal model, and aftereffects formed along the same path as that observed when the subjects were learning B for the first time.

DISCUSSION

We previously observed that, when young, normal subjects practiced reaching movements in a force field, they formed an internal model of that field (Shadmehr and Mussa-Ivaldi 1994b). Associated with this motor memory was a functional component that strongly biased the ability of subjects to form internal models of subsequent force fields (Shadmehr et al. 1995). Within a few hours, this bias declined and the subjects could learn the second field nearly as well as naive subjects (Brashers-Krug et al. 1996). In a declarative memory task that shared some features of our motor task, subjects learned to associate word A to word B, followed by A-C pairing. In normal subjects, learning of A-C can be more difficult than learning A-B (Underwood 1949). AMN subjects are impaired in learning the A-B association (Van der Linden et al. 1993; Winocur and Weiskrantz 1976). Once they learn it, however, they exhibit a greater than normal amount of difficulty in learning A-C (Winocur et al. 1996; Van der Linden et al. 1993). In a task that required remembering the location of visually presented spatial targets, subjects with frontal lobe lesions displayed greater than normal amounts of difficulty in learning when the same targets appeared in new locations (Smith et al. 1995). The delayed match-to-sample paradigm was used in monkeys with medial temporal lobe (MTL) lesions to serve as an animal model of human AMN (Alvarez et al. 1994). In this task, anterograde interference was reported (Worsham 1975) and shown to be increased with damage to the MTL (Owen and Butler 1984). Therefore damage to a loosely defined declarative memory system can magnify the normal interference associated with learning of certain declarative associations. What affect does impaired declarative memory have on the interference associated with motor memories?

On day 1, subjects learned field A. We found that the AMN subjects, including *H.M.*, formed internal models of the mechanical dynamics of arm movements at a normal rate, had aftereffects, and maintained the aftereffects for at least a 24-h period. This result was evidence for a long-term

motor memory for A. On session 1 of day 2, subjects learned field B and at 5 min were retested in A. Normal subjects began relearning/recall of A with aftereffects that showed instantiation of an internal model appropriate for B, i.e., perseveration. As a result, performance in A was significantly worse than their own performance when they were naive. Our group of AMN subjects displayed a similar behavior. They learned B and had aftereffects, and these aftereffects for B were present as they attempted to make reaching movements in field A. Their performance in A was now significantly worse than what we observed when they were naive. It appears therefore that the anterograde interference associated with learning of reaching movements occurs despite AMN and despite significant damage to the MTL as was the case with *H.M.*

The persistence of aftereffects demonstrates that, when the motor memory system recently learned an internal model that is inappropriate for the current field, performance will be worse than naive. This is despite the fact that on session 1 of day 2, field A was the same field for which long-term retention was demonstrated. Therefore learning of B interfered with recall of A. In principle this interference may be caused by at least two factors. First, learning B could disrupt consolidation of A, resulting in retrograde interference. Because the temporal distance between learning of the two fields was 18 h, other experiments suggest that this is unlikely (Shadmehr and Brashers-Krug 1997). Second, learning of B may engage a component of motor memory that was also engaged when A was recalled (e.g., a hypothetical part of the motor memory system that may be used for on-line control), resulting in anterograde interference. The current experimental design however cannot distinguish between these two factors that can combine to affect performance in a test of recall. We can only state that decrements in performance were observed in both groups and that the magnitude of the decrements did not differ significantly.

To investigate time-dependent properties of interference, we considered a situation in which interference was reduced in magnitude compared with that observed during session 1 of day 2. Four hours after completion of session 1 of day 2, subjects were again presented with field B (session 2). In normal subjects, we expected that the passage of time should result in a fading of the anterograde interference that is associated with A. We thought therefore that performance in B should show little aftereffects for the internal model appropriate for A. The performance of normal subjects in B was nearly identical to their naive performance, and their aftereffects now showed little influence of A, i.e., significantly reduced perseveration. The AMN subjects also showed aftereffects that displayed little persistence of A, and their performance was not significantly different from their naive performance. Therefore, although at 5 min the anterograde interference associated with motor memory of a field was strong, at 4 h this interference was less. All subjects displayed this pattern.

Although we could not distinguish AMN and normal subjects based on the interference associated with acquiring motor memories, there were significant differences between the performance of subject *H.M.* and that of other subjects. *H.M.* moved slower and intriguingly had significant difficulties in performing the spatial kinematic transformation

that is required in this task, to associate a visually presented target to a motion of the hand toward that target (Fig. 1). Note that the plane of hand movements was perpendicular to the plane on which the cursor moved. With extended practice in the initial experimental session, this performance improved significantly and was maintained throughout the 2-day experiment.

The difference between the performance of *H.M.* and that of other subjects may be caused by a number of factors. First, *H.M.* has reduced proprioceptive sense in his arm because of a slight case of medication-related sensory neuropathy (Hebben et al. 1985). It is known that severe loss of proprioception from the arm results in directional errors in visually targeted arm movements (Gordon et al. 1995). However, because *H.M.*'s sensory loss was not severe (Hebben et al. 1985), and because he slowly improved with practice and was able to maintain his performance over a 24-h period, it seems unlikely that sensory neuropathy was the main cause of the difference. Second, *H.M.* has marked cerebellar atrophy (Corkin et al. 1997). Patients with cerebellar lesions have reduced abilities to learn visuomotor transformations and exhibit little or no aftereffects in prism adaptation experiments (Gauthier et al. 1979; Thach et al. 1992; Weiner et al. 1983). *H.M.* however had normal aftereffects in the phase of the task that required learning mechanical dynamics.

H.M.'s motor learning deficit was restricted to acquiring the spatial kinematic transformations of the task. It is possible that this component of our task is part of a class of behaviors termed conditional motor learning (Passingham 1993), where a visual stimulus that may or may not have relevant spatial information is learned to be associated with a direction of movement (Wise 1996). Intriguingly, monkeys with bilateral lesions of the hippocampus learn a conditional motor task, for example, associating arbitrary visual cues to directions of arm movement, at rates that are significantly slower than those of control monkeys (Murray and Wise 1996). Our observation in *H.M.* is reminiscent of this finding. Studies of subjects with MTL lesions who have no cerebellar disorders will clarify whether this component of reaching movements is dependent on the integrity of MTL structures.

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