

Direct Comparison of Neural Systems Mediating Conscious and Unconscious Skill Learning

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Direct comparison of neural systems mediating conscious and unconscious skill learning. *J Neurophysiol* 88: 1451–1460, 2002; 10.1152/jn.00461.2001. Procedural learning, such as perceptual-motor sequence learning, has been suggested to be an obligatory consequence of practiced performance and to reflect adaptive plasticity in the neural systems mediating performance. Prior neuroimaging studies, however, have found that sequence learning accompanied with awareness (declarative learning) of the sequence activates entirely different brain regions than learning without awareness of the sequence (procedural learning). Functional neuroimaging was used to assess whether declarative sequence learning prevents procedural learning in the brain. Awareness of the sequence was controlled by changing the color of the stimuli to match or differ from the color used for random sequences. This allowed direct comparison of brain activation associated with procedural and declarative memory for an identical sequence. Activation occurred in a common neural network whether initial learning had occurred with or without awareness of the sequence, and whether subjects were aware or not aware of the sequence during performance. There was widespread additional activation associated with awareness of the sequence. This supports the view that some types of unconscious procedural learning occurs in the brain whether or not it is accompanied by conscious declarative knowledge.

INTRODUCTION

Procedural learning refers to learning that is governed by rules or procedures, for example, perceptual-motor skills. It can be contrasted with declarative learning of facts or events (Cohen and Squire 1980). Procedural memory can be gained without conscious awareness of the rules being learned, whereas declarative memory is characterized by conscious awareness of the facts or events being learned. Procedural learning is thought to reflect learning by doing: experience-based tuning of the neural systems used to perform the perceptual-motor task (Karni et al. 1995; Willingham 1998). Procedural learning is also thought to be neurally independent of declarative memory (Cohen and Squire 1980; Squire 1992). The strongest evidence for this view comes from neuropsychological studies in which patients with global amnesia exhibit completely intact skill learning despite severely impaired declarative memory (Cohen and Squire 1980; Milner 1962; Nissen and Bullemer 1987). Conversely, patients with injuries in

motor systems that subserve performance exhibit impaired skill learning (Gabrieli et al. 1997; Heindel et al. 1988; Willingham et al. 1996).

The serial response time task (SRTT) is one task used to study procedural learning. In this task, a target appears in one of four horizontal locations. The subject's task is simply to press the button below the location in which the target appears on each trial. Unbeknownst to the subject, the target locations are sometimes determined by a repeating sequence and other times randomly. With practice, subjects show perceptual-motor sequence learning by performing faster on the repeating sequence than on random locations; this difference can only be accounted for by sequence-specific skill.

The SRTT offers an exceptionally well-controlled opportunity to compare procedural and declarative learning because it can be manipulated to be an implicit or an explicit task. An implicit task is one in which the experimenter makes no reference to an earlier learning episode; learning is assessed by the subject's performance on a task (e.g., response time performance in the SRTT). In an explicit task, the experimenter does refer to an earlier learning episode and directly queries the subject's memory (Graf and Schacter 1985). Implicit tasks are designed to invoke procedural memory, and explicit tasks are designed to invoke primarily declarative memory.

The SRTT can be administered as an implicit task in which the subject is never told about the sequence. Under these conditions, the sequence is learned procedurally, as evidenced by normal learning by amnesic patients (Nissen and Bullemer 1987; Reber and Squire 1994, 1998). Amnesic patients and normal subjects have been shown to learn the sequences without being aware of them (Reber and Squire 1994; Reed and Johnson 1994). Evidence for this comes from chance performance by amnesic and normal subjects on an explicit memory test of the sequence learned in the prior implicit task.

The SRTT can reflect declarative learning, however, when it is administered as an explicit task. Subjects are told that the stimuli are sequenced and that they are to learn the sequence. Declarative knowledge of the sequence results in faster performance as subjects consciously anticipate the location of each successive target (Curran and Keele 1993; Willingham et al. 1989). Subjects may also become aware of the sequence spontaneously, even if explicit instructions are not part of the task.

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In other procedural learning paradigms, such as rotary pursuit and mirror tracing, declarative memory usually does not make a contribution; declarative memory does not appear to affect performance or the rate of learning, as evidenced by the normal rate of learning by patients with declarative memory impairments (Gabrieli et al. 1993; Heindel et al. 1989).

Many other perceptual-motor learning paradigms are always explicit and likely always involve declarative learning. In such paradigms, subjects memorize sequences of key presses or finger movements through explicit instruction (Jenkins et al. 1994; Jueptner et al. 1997a; Karni et al. 1995). For example, one functional neuroimaging study (Jueptner et al. 1997b) compared activation for memorized sequences performed with versus without attention to the component movements. Attention was manipulated by experimenter instruction. Subjects first learned the sequence of key presses through trial and error with auditory feedback. They continued to practice it, prior to being scanned, for over 30 min *after* they were able to perform it without any errors. During scanning, movements were paced by a tone; there were no indicators of which keys to press. Subjects were able to perform the sequence without attention to the movements because it had been practiced to the point of automatization. Skilled performance on tasks like this may involve procedural as well as declarative learning, but explicit knowledge of the sequence is critical for performing the task. Consequently, it is impossible to know whether to interpret functional neuroimaging activation as procedural or declarative in nature or as a combination of both.

Four functional neuroimaging studies have compared brain activation associated with procedural learning versus declarative learning in the SRTT. In two of the studies, subjects repeatedly responded to one sequence (Honda et al. 1998; Rauch et al. 1995). The declarative learning phase began after they became aware of the sequence through repetition (awareness was measured between every block) or direct instruction. The other two studies also measured procedural and declarative learning sequentially, but they used two different sequences (Grafton et al. 1995; Hazeltine et al. 1997). Awareness was reduced in the procedural learning phase because subjects had to attend to a secondary task, tone counting. In the absence of the secondary task in the declarative phase, subjects easily became aware of the six-element sequence. Remarkably, all four studies found that entirely different neural networks were activated during procedural versus declarative sequence learning. Thus when subjects had declarative knowledge of the sequence, the neural systems underlying procedural learning appeared to show no learning at all (i.e., there were no changes in activation over time) even though perceptual-motor practice occurred in both cases. These studies indicate that if learning occurs declaratively in SRTT, then plasticity occurs only in neural systems that are not involved in procedural learning.

These uncontroverted findings challenge the idea that procedural skill learning is an obligatory consequence of experience. They also contradict behavioral evidence that procedural learning occurs during declarative learning (Willingham and Goedert-Eschmann 1999). In that SRTT study, subjects learned a sequence either declaratively, after instructions to learn the sequence as they responded, or procedurally. A free recall test verified that subjects could consciously recall the sequence under explicit instructions, but not implicit. After learning the sequence, subjects were told that during a transfer phase they

would respond to all randomly ordered locations to obtain a baseline response time. In fact, either the sequence seen during training or a new sequence was repeated several times within a block of otherwise randomly ordered locations. Response times were faster to the trained sequence than to the surrounding random stimuli. This response time advantage was not observed if the sequence was new, but was equally robust if the sequence had been learned procedurally or declaratively. Critically, subjects' subsequent confidence ratings on whether they had responded to an old or new sequence in the supposedly random transfer block showed that they were not aware that the old sequences were present. Therefore the learning shown at transfer must have been supported by procedural memory, even for those subjects who only received declarative training on the sequence; if these subjects had recruited declarative memory during transfer, they would have been aware that the sequence was present. The confidence ratings, however, showed that subjects did not have such a recollection. Thus subjects simultaneously gained procedural memory for a sequence while they learned the same sequence declaratively.

The discrepancy between the imaging and behavioral results may be attributable to several factors. First, the conclusion that neural areas are unique to procedural learning relies on null results—these areas are not seen in declarative learning. Second, measuring procedural and declarative activation sequentially as subjects become aware of the sequence, as did two of the previous imaging studies (Honda et al. 1998; Rauch et al. 1995), confounds order, amount of practice, and performance levels with the change in awareness. There is more practice in the declarative condition because it always occurs after the procedural condition has terminated. Furthermore, performance is always superior in declarative learning conditions for such tasks. Using two different sequences, as did the other two studies (Grafton et al. 1995; Hazeltine et al. 1997), controls the amount of practice on each sequence (but not performance levels), but confounds the procedural/declarative distinction with the presence or absence of a secondary task. Behavioral evidence indicates that the tone counting task disrupts performance, but not learning, in procedural sequence learning (Frensch et al. 1999). This additional behavioral dimension might have affected the neural activity in the implicit condition in these studies.

We therefore used fMRI to discover whether declarative learning does or does not prevent learning in procedural memory systems. We created conditions in which subjects were simultaneously learning different sequences under implicit or explicit instructions. To our knowledge, no prior imaging study has created conditions that allow for such direct comparison of simultaneous procedural and declarative learning. Then, we interrogated the procedural system that mediated learning without awareness to discover whether it had also mediated learning for the sequence learned declaratively.

Subjects were explicitly instructed that red circles denoted a repeating sequence of locations and that black circles denoted a random ordering of locations. Prior to scanning, subjects responded to a single repeating sequence that always determined the location of the red circles. This sequence constituted the "explicit-overt" condition because subjects were aware of the repeating sequence appearing in red. Prior to scanning, subjects also responded to black

circles. Unbeknownst to subjects, some black circles actually appeared in a second repeating sequence (the others appeared in random locations). This sequence constituted the “implicit” condition because subjects were unaware that there was a repeating sequence for black circles. Thus prior to scanning, subjects simultaneously learned one sequence explicitly and another sequence implicitly (Table 1).

During scanning, there were four conditions. The “explicit-overt” condition presented again the repeating red-circle sequence. We anticipated that this condition would engage brain areas previously implicated in declarative sequence learning. The other three conditions involved black circles. The “implicit” condition presented the second sequence learned without awareness prior to scanning. This was expected to activate brain areas previously implicated in procedural sequence learning. The “random” condition presented circles in random locations and constituted the baseline condition. The critical manipulation was the fourth, “explicit-covert” condition in which the same sequence used for the “explicit-overt” condition appeared disguised as black circles. Thus subjects were performing the identical actions in identical sequence for the “explicit-overt” and “explicit-covert” conditions; the two differed only by the colors of the stimuli with red circles signaling the presence of the explicitly learned sequence and black circles camouflaging the presence of the same sequence. Thus these were identical motor sequences that differed only by the presence or absence of conscious awareness of the sequence.

Response times were expected to differ by condition. Responses in the explicit-overt condition should be the fastest, because subjects can consciously anticipate subsequent locations. Responses in the explicit-covert condition should be faster than in the random condition, demonstrating skill, but slower than in the explicit-overt condition. Response times should be slower than in the explicit-overt condition because subjects’ lack of awareness should prevent them from anticipating subsequent locations. Responses in the implicit condition should likewise be faster than in the random condition, but not differ from those in the explicit-covert condition.

The central question was whether the procedural neural system (identified by the implicit condition) would show evidence for having learned the same explicit sequence that was learned with awareness. This would be demonstrated by the “explicit-covert” condition, yielding activation in the procedural system. If such activation were found, it would argue that procedural learning for sequence tasks occurs during the course of declarative learning as an obligatory consequence of experience. If such activation is not found, it would support the implication of prior studies that declarative learning prohibits procedural learning for sequence tasks.

TABLE 1. *Experimental paradigm*

Phase	Implicit	Explicit-Overt	Explicit-Covert	Random
Training (pre-scan)	Sequence 1	Sequence 2	—	Random
Test (in scanner)	Sequence 1	Sequence 2	Sequence 2	Random

Note: Conditions changed every 24 trials (after 2 sequence repetitions).

METHODS

Subjects

Twenty-two right-handed volunteers (aged 19–30 years; 13 males and 9 females) participated after providing informed consent. Four subjects (3 male) were excluded from analyses because they learned neither the implicit nor the explicit sequence. All subjects provided informed consent for the study, which had approved by the Institutional Review Board.

SRTT paradigm

A 3/4-in. diam circle appeared in one of four (1 in. × 1 in.) squares arranged horizontally in the middle of the computer screen. Subjects pressed the response key (in a row of 4) with the index and middle finger of both hands, each finger mapped to a key. Each stimulus stayed on the screen for 600 ms with a 250-ms interstimulus interval.

Sequences (each 12-units long) were randomly chosen for each subject from a corpus of 576 sequences, each of which followed the following constraints: equal frequency of each position, no direct repetitions, and no runs (e.g., 1234) or trills (1212) of more than three positions in a row.

Stimuli were presented in blocks of 24 with a 2.2-s inter block interval. Each block started with a 520-ms fixation mark (a cross) between the middle two boxes. The first circle appeared 800 ms after the disappearance of the cross. Each block consisted of two repetitions of one type of sequence (Table 1). The starting positions of each repeating sequence was randomly chosen for each block to minimize the likelihood of subjects’ gaining declarative knowledge in the implicit condition.

Prescan training

Instructions were to respond quickly and accurately and learn the 12-unit red sequence. Subjects were told that the sequence starting position varied for each new block. Subjects performed 24 implicit blocks, 24 explicit blocks, and 6 random blocks prior to scanning, and a further 8 implicit blocks, 8 explicit blocks, and 2 random blocks during anatomical scans. Condition order was random within sets of 9 blocks (4 explicit-overt, 4 implicit, and 1 random block).

Test

During functional scans, subjects responded to 16 implicit, 8 explicit-overt, 8 random, and 8 explicit-covert blocks. The implicit condition used the sequence that was used during implicit training. The explicit-overt and explicit-covert conditions both used the explicit sequence that was used in training. The explicit-overt condition presented this sequence in red, but the explicit-covert condition presented it using black circles, so that subjects would not necessarily recognize it as the sequence that they had earlier learned declaratively. The sequences used during training and test are shown in Table 1.

Sixteen implicit blocks were used to match the total number of explicit sequence repetitions. The order of conditions was random within sets of five blocks (1 explicit-overt, 1 explicit-covert, 1 random, and 2 implicit blocks).

Postscan recognition test

The recognition test took place in the scanner after the test phase, but imaging was not performed during this task. The purpose was to ensure that subjects indeed gained declarative knowledge of the explicit sequence, but not of the implicit sequence. Stimuli were blue to eliminate color cues. Subjects responded to one explicit, one implicit, and four random blocks, each identical in structure to those used in the test phase. Instructions were to respond to each circle quickly and accurately by hitting the appropriate key and then to rate

the likelihood of having seen that particular sequence before. Subjects were encouraged to take their time rating. Ratings were made on a scale of 1 (definitely have not seen it) to 4 (definitely have seen it). The endpoint labels were on the rating screen.

Imaging protocol and analysis

Whole-brain imaging was performed on a 3T MRI Signa LX Horizon Echosped (G. E. Medical Systems, 8.2.5 systems revision). T2-weighted spin-echo anatomical images (TR = 3000, TE = 80) were acquired in 30 contiguous 6-mm coronal slices. Functional images were acquired in the same set of slices by using a T2*-sensitive gradient echo spiral pulse sequence (Glover and Lai 1998) with parameters of one interleave, 30-ms TE, 2,200-ms TR, 78° flip angle, 20-cm field of view, and 64 × 64 data acquisition matrix. A high-resolution three-dimensional (3D) SPGR volume was also collected for use in spatial normalization.

Functional images were motion-corrected using AIR 3.0 with interpolation to 3-mm cubic voxels (Woods et al. 1992). All further data processing and analyses were conducted with SPM99 (Wellcome Department of Cognitive Neurology, London, UK). Images were spatially normalized to MNI space (which uses the same orientation and origin as the Talairach atlas; Talairach and Tournoux 1988), smoothed with a Gaussian filter (6-mm full-width half-maximum), and filtered to remove low-frequency components.

Effects of each condition were estimated separately for each subject according to the general linear model at each voxel (Friston et al. 1995). Images taken during the 2.2-s inter block interval were not included in the model. Statistical parametric maps of voxel values (contrast images) were formed for each comparison of interest. These images served as dependent variables in one sample *t*-test for each effect of interest (i.e., random effects model) (Holmes and Friston 1998).

Regions of interest (ROIs), selected from implicit sequence learning neuroimaging studies, were used to identify regions active in procedural learning (implicit minus random) (Berns et al. 1997; Grafton et al. 1995, 1998; Hazeltine et al. 1997; Honda et al. 1998; Peigneaux et al. 2000; Rauch et al. 1995, 1997). All reported activations in more than one publication were included: right putamen, left putamen, right caudate, left caudate, left Brodmann's area (BA) 46, left inferior parietal cortex, left supplementary motor area (SMA), left central sulcus, left post-central sulcus, left superior parietal cortex, left anterior cingulate, left BA 10, and left occipital gyrus (BA 18). ROIs were the total volume encompassed by 2,000-mm³ spheres around each published coordinate.

Statistical thresholds ($P < 0.05$) were corrected for the number of comparisons (voxels) in the search volume in each analysis. SPM99s small volume correction was employed within each ROI (Worsley et al. 1996). When we were specifically interested in whether regions active in one condition were also active in a second condition, we restricted search volumes to significant regions found in the first condition.

We accepted as significant voxels and clusters that exceeded corrected thresholds (Friston et al. 1994). To obtain neuroanatomically interpretable levels of spatial resolution, we set the height threshold for clusters at $P < 0.001$ (uncorrected) for non-a priori neural regions. Because ROIs are spatially constrained, we set the height threshold for clusters at $P < 0.05$ (uncorrected).

RESULTS

Behavioral results

TEST PHASE. During scanning, mean accuracy was high [$92.7 \pm 1.5\%$ (SD)] and did not differ among conditions, $F(3,51) < 1$ [repeated measures analysis of variance (ANOVA)].

Response times were summarized by finding the median response time of each set of 12 responses, yielding eight medians for each trial block for each subject. The mean of these eight medians was calculated, which served as the summary response time measure for each trial block for each subject. A repeated measures ANOVA on the means with condition as a repeated factor showed a reliable effect of condition, $F(3,51) = 22.91$, $P < 0.001$. Planned contrasts showed that subjects were faster than random in the explicit-overt $F(1,17) = 38.44$, $P < 0.001$; explicit-covert $F(1,17) = 14.33$, $P < 0.005$; and implicit conditions $F(1,17) = 19.74$, $P < 0.001$ (Fig. 1). Subjects were also faster in the explicit-overt condition than in the explicit-covert $F(1,17) = 24.11$, $P < 0.001$ or implicit conditions $F(1,17) = 20.20$, $P < 0.001$, which did not differ from each other, $F(1,17) = 1.42$, $P > 0.20$.

Separate repeated measures ANOVAs were conducted on the means from each block to compare response time (RT) changes in each of the three sequence conditions to RT changes in the random condition. Block (8) and condition (2) were repeated factors. No new learning occurred in the test phase; block by condition interactions were not significant ($P > 0.20$), indicating no changes in RT relative to random blocks.

POSTSCAN RECOGNITION TEST. A repeated measures ANOVA on the mean ratings showed a reliable effect of condition, $F(2,34) = 13.32$, $P < 0.001$. Planned contrasts showed that ratings for the explicit sequences (3.4 ± 1.0) were higher than those for implicit (2.3 ± 0.8) $F(1,17) = 11.02$, $P < 0.005$ or random sequences (2.0 ± 0.5) $F(1,17) = 21.36$, $P < 0.001$. Ratings did not differ between the implicit and random sequences ($P > 0.10$).

RTs as subjects performed each sequence immediately prior to rating it were also recorded. These data were lost for two subjects, due to technical difficulties. A repeated measures ANOVA on the mean of the medians from the 12 RTs in each repetition showed a reliable effect of condition, $F(2,30) = 11.70$, $P < 0.001$. Planned contrasts showed that subjects were faster to explicit (284 ± 87.1) than implicit sequences (331 ± 43.6) $F(1,15) = 8.22$, $P < 0.05$, and faster to implicit than random sequences (346 ± 50.2) $F(1,15) = 5.97$, $P < 0.05$.

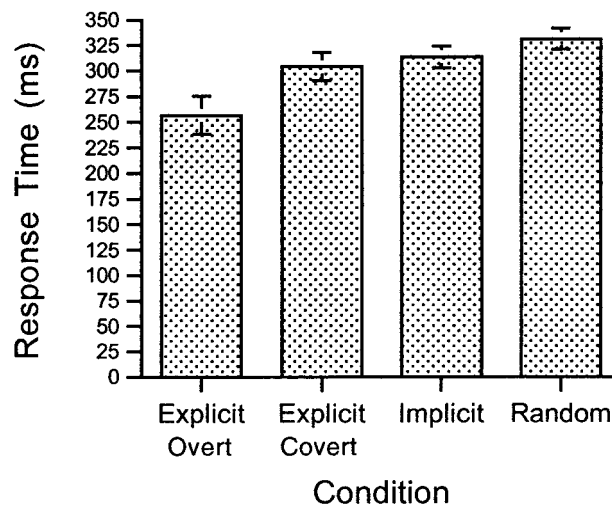


FIG. 1. Mean response time (RT) for each condition during the test phase in the scanner. Error bars show SE.

Imaging results

REGIONS ACTIVE IN PROCEDURAL MEMORY. ROIs with greater activity ($P < 0.05$) in the implicit than random condition were the left inferior frontal gyrus (BA 46 and BA10), right putamen, and left inferior parietal cortex (BA 40) (Fig. 2A, Table 2). No regions outside of the ROIs met the corrected threshold ($P < 0.001$).

All active regions in the implicit condition were also active in the explicit-covert condition, except that the active region of left inferior/middle frontal gyrus did not extend to BA 10 in the explicit-covert condition (Fig. 2B, Table 2). Reverse comparisons (R-I, R-EC) yielded no activations. Comparisons within procedural regions between the implicit and explicit-covert conditions showed no significant difference in the degree of activation in either the putamen or BA 10, but there were differences in BA 40 (I > EC) and 46 (EC > I). No regions differed between the two conditions when the search volume included the entire brain.

REGIONS ACTIVE IN DECLARATIVE MEMORY. Regions active in the implicit and explicit-covert conditions were also active in the explicit-overt condition (relative to random), except for the region of left inferior parietal cortex (Fig. 2C, Table 3). Activity was greater in this region in both the explicit-covert and the implicit conditions than in the explicit-overt condition.

TABLE 2. Regions active in procedural memory

Brain Region	Implicit > Random†		Explicit-Covert > Random††	
	x, y, z	t Score	x, y, z	t Score
R. putamen	27 0 3	3.65	24 -3 6	2.45
L. inferior parietal (40)	-45 -20 18	2.97	-45 -17 17	2.25
L. inf/mid frontal g. (46)	-42 33 12	2.92	-45 33 15	4.37
L. inf/mid frontal g. (10)	-36 47 0	2.48		

Talairach coordinates are for peak voxels [throughout the paper, converted from MNI coordinates (<http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html>)]. *t* Scores were significant at the cluster level $P < 0.05$, corrected for the number of voxels in the search volume.

† Search volumes restricted to each ROI.

†† Search volume restricted to significant voxels in implicit > random comparison.

Prefrontal activation, however, was greater in the explicit-overt condition than in the implicit condition (BA 46 and 10) or the explicit-covert condition (BA 10).

Over the whole brain, many areas were more active in the explicit-overt condition than in the other conditions. Activated regions, relative to the random condition, included bilateral superior parietal cortex, bilateral cerebellar cortex, brain stem, bilateral middle frontal and inferior frontal gyri, cingulate gyrus, right caudate, and bilateral premotor cortex (Fig. 3, Table 3). Comparisons between the explicit-overt and explicit-covert and implicit conditions yield very similar results (Table 3). It is particularly notable that many regions were more active in the explicit-overt than the explicit-covert condition, despite the fact that the sequences were identical.

Two regions were more active in the random than the explicit-overt condition: medial dorsal frontal gyrus (BA 10) and posterior cingulate gyrus (BA 23/30). Regions more active in the implicit than the explicit-overt condition were the bilateral parietal-temporal junction, left supramarginal gyrus, and posterior cingulate gyrus (BA 23/30). Similar regions [bilateral parietal-temporal junction, posterior cingulate gyrus (BA 23/30), and dorsal frontal gyrus (BA 9)] were also more active in the explicit-covert than the explicit-overt condition.

Correlations

Correlations between performance (RTs) or learning (random minus sequence RTs) and activation were performed within the four regions identified as active in procedural memory. Faster subjects showed more activity in left BA 40. Correlations in this region between RTs and signal values were significant for random ($r = -0.59$), implicit ($r = -0.65$), and explicit-covert sequences ($r = -0.56$; $P < 0.05$), and marginal for explicit-overt sequences ($r = -0.41$; $P < 0.10$). In BA 46, subjects who showed the greatest RT benefit in the explicit-overt sequences showed the least activity during the explicit-overt condition (both measures relative to random), $r = -0.53$ ($P < 0.05$).

DISCUSSION

The present behavioral results demonstrate that 1) subjects were conscious of the explicit sequence; 2) unconscious of the implicit sequence; and 3) unconscious of the explicit sequence when it appeared covertly in black. First, subjects were aware

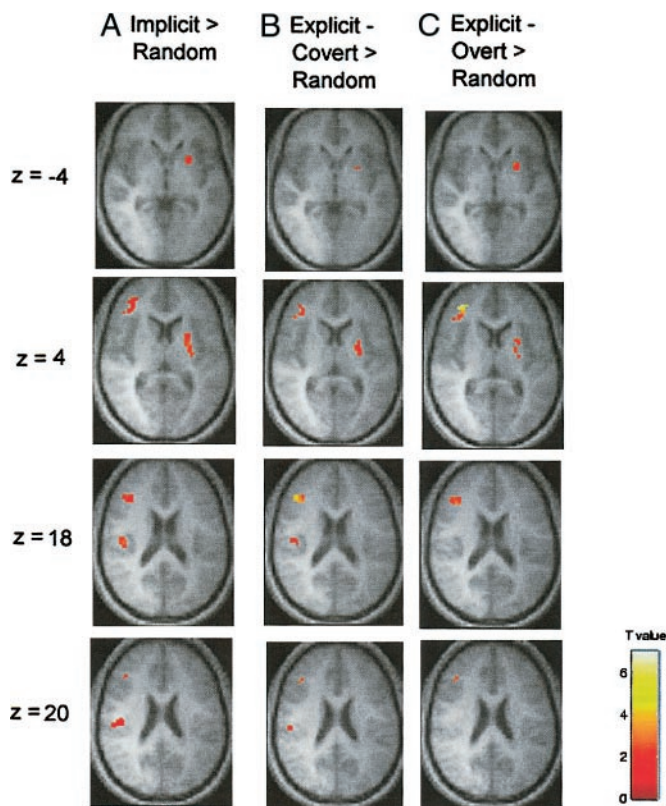


FIG. 2. Regions active in procedural memory. A: regions more active in the implicit than the random condition: left Brodmann's area (BA) 10 and 46, right putamen, and left inferior parietal cortex (cluster level $P < 0.05$; height threshold $P < 0.05$ uncorrected), corrected for the number of voxels in each region of interest). B: regions more active in the explicit-covert than the random condition: left BA 46, right putamen, and left inferior parietal cortex (search volume restricted to significant voxels in A). C: regions more active in the explicit-overt than the random condition: left BA 10 and 46 and right putamen (search volume restricted to significant voxels in A).

TABLE 3. *Regions active in declarative memory*

Brain Region	Explicit-Overt > Random†		<i>t</i> Score	Explicit-Overt > Random††		<i>t</i> Score	Explicit-Overt > Explicit-Covert††		<i>t</i> Score	Explicit-Overt > Implicit††		<i>t</i> Score				
	<i>x</i>	<i>y</i>		<i>x</i>	<i>y</i>		<i>x</i>	<i>y</i>		<i>x</i>	<i>y</i>					
R. post. parietal (7/40)				33	-56	53	9.60*	36	-68	45	6.54	33	-58	58	7.07	
L. post. parietal				33	-56	53+						33	-58	58+		
Precuneous				33	-56	53+		-12	-67	50	5.21	33	-58	58+		
Ant. cingulate (32/SMA)				3	22	40	7.23					3	20	40	5.63	
Mid. cingulate (23)				3	-28	29	5.81					3	-31	29	5.64	
Post. cingulate (31)				18	-24	37	5.46									
L. mid. frontal (46/10)	-40	28	18	3.19	-36	47	3	6.91	-42	47	9	4.70	-42	50	9	5.42
	-36	47	3	6.91*												
L. mid. frontal (6)				-24	14	52	6.09									
R. mid. frontal (10)				33	61	-8	6.97	36	50	3	4.14	50	13	35+		
R. mid. frontal (9)				33	61	-8+		50	22	38	4.60	50	13	35	6.62	
R. mid. frontal (6)				33	61	-8+		33	11	46	4.59	50	13	35+		
L. inf. frontal (45)				-39	18	2	6.47					-42	18	2	5.42	
R. inf. frontal (47)				33	23	-4	6.74	33	26	-4	4.55	48	18	7+		
R. inf. frontal (45)				33	23	-4+		50	15	2	5.29	48	18	7	6.74	
R. caudate				12	3	5	6.89	12	-9	-5+		18	-5	14	8.52*	
R. putamen	27	-5	11	3.62												
R. globus pallidus								12	-9	-5	6.10					
R. thalamus				12	3	5+		12	-9	-5+		18	-5	14+		
L. globus pallidus								-15	-6	3	5.73					
L. thalamus				-6	-9	0	6.91					18	-5	14+		
Brainstem				6	-30	-16	6.36	-6	-30	-9	5.61	3	-30	-16	6.76	
Cerebellar vermis								0	-60	-25	5.97					
L. cerebellum				-30	-62	-22	7.44	-27	-65	-22	7.17					
R. cerebellum				33	-68	-14	5.85	36	-51	-20	6.70					
								36	-60	-37	5.85					
L. fusiform (19)												-27	-73	-6	6.76	
R. fusiform (19)												33	-73	-6	5.39	

Talairach coordinates *x*, *y*, *z*, are for peak voxels. Coordinates followed by '+' indicate that the cluster's extent included the region. All *t* scores were significant at the cluster level $P < 0.05$, corrected for the search volume.

† Search volume restricted to significant voxels in the implicit > random comparison.

†† Search volume included entire brain.

* Also significant at the voxel level, $P < 0.05$, corrected.

of the sequence in the explicit-overt condition. Throughout scanning, they performed it faster than the random or implicit sequences. They also learned it declaratively, indicated by the fact that they selected it among the distracters (random and implicit sequences) in the postscan recognition test as a se-

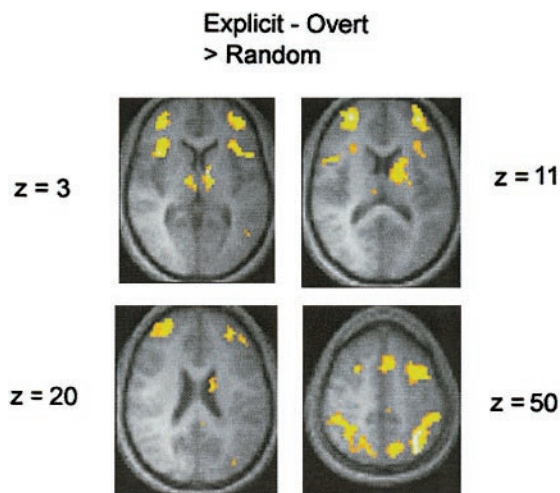


FIG. 3. Regions active in declarative memory. Regions more active in the explicit-covert than the random condition (cluster level $P < 0.05$, height threshold $P < 0.001$ uncorrected), corrected for number of voxels in the brain. Slices show activation in bilateral prefrontal cortex (BA 10, 46, 45, and 9), bilateral premotor cortex, right thalamus/caudate, supplementary motor area (SMA), and bilateral posterior parietal cortex.

quence they had seen before. Second, subjects learned the sequence procedurally in the implicit condition. They responded faster to the implicit sequence than to the random sequences, but slower to it than to the explicit sequence. Nevertheless, even at the end of the experiment, they failed to recognize the implicit sequence above chance. The postscan recognition test was designed to be highly sensitive to any awareness of the sequence: a graded rating scale was used so subjects could show even partial declarative knowledge. Furthermore, subjects made the recognition judgments simultaneously with performing the sequences, showing a concurrent dissociation between their procedural (RTs faster than random) and declarative knowledge (no difference from random sequences). These objective and sensitive measures go well beyond the self-report measures used in most other studies of implicit sequence learning. Finally, subjects were not aware of the explicit sequence in the explicit-covert condition. RTs did not differ between the implicit and explicit-covert conditions. Also, subjects were slower in the explicit-covert than in the explicit-overt condition, despite making identical responses to identical sequences. We were able to achieve this level of nonawareness in the implicit and explicit-covert conditions by using a very high proportion of random sequences, few repetitions, and frequent changes among conditions and sequence starting places throughout the study (relative to other sequence learning studies).

Considered together, the behavioral and neuroimaging re-

sults from this study demonstrate that procedural learning in this paradigm is an obligatory consequence of performance. In the present paradigm, procedural memory (implicit greater than random condition) activated left prefrontal cortex, left inferior parietal cortex, and right putamen. The same regions were also active in the explicit-covert condition in which the sequence had been *declaratively* learned. Although the degree of activation differed in some of these structures, the neural network that enhanced performance for the implicit and for the explicit-covert conditions was virtually the same. The explicit-covert activation, therefore, documents procedural modulation that occurred under conditions of declarative learning and awareness in the prescan skill learning session.

Procedural learning in other paradigms—especially ones in which the learning is not motoric—may well not be a consequence of performance alone, but may be affected by ongoing declarative learning. For example, Poldrack and his colleagues (1999, 2001) report that neural systems supporting declarative and procedural learning of a probabilistic categorization task actually compete, rather than operate in parallel. However, this procedural task is not based on motor skill. Further, amnesic patients perform normally only in the early phase of this task (Knowlton et al. 1994), a finding that suggests that declarative memory plays a role in this task. Other motor skill studies have indicated that declarative learning may affect procedural learning. For example, Shea and Wulf (1999) reported that attention to the biomechanics of a movement retarded learning. However, these declarative manipulations may well change the performance of the task; if learning closely follows performance, as we have suggested, then one would expect that any manipulation that affects performance will affect learning as well.

Regions activated for procedural and declarative learning in this study were consistent with those reported previously in the SRTT (Grafton et al. 1995; Hazeltine et al. 1997; Peigneux et al. 2000; Rauch et al. 1997), but we found fewer procedural regions and much more overlap between activations than others have reported (Grafton et al. 1995; Hazeltine et al. 1997; Honda et al. 1998; Rauch et al. 1995). Areas activated in procedural learning in other studies, including the SMA (Grafton et al. 1995; Hazeltine et al. 1997), sensorimotor (Berns et al. 1997; Grafton et al. 1995, 1998; Hazeltine et al. 1997; Honda et al. 1998) and premotor cortex (Rauch et al. 1995, 1997), and the caudate (Peigneux et al. 2000; Rauch et al. 1995, 1997), were not activated. All these areas, except sensorimotor cortex, were activated in the explicit-overt condition. Regions were also activated in the explicit-overt condition that have been reported for declarative sequence learning, including the precuneus (Sakai et al. 1998), bilateral dorso-lateral prefrontal cortex (BA 9,10, and 46) (Grafton et al. 1995; Jueptner et al. 1997a; Sakai et al. 1998), right premotor cortex (Grafton et al. 1995; Hazeltine et al. 1997; Honda et al. 1998), right inferior frontal gyrus (BA 45) (Hazeltine et al. 1997), right caudate (Jueptner et al. 1997a), and the brain stem (Rauch et al. 1995). This consistency between the present and past findings suggests that novel features of the present design, such as simultaneously learning two sequences, did not substantially alter learning associated neural activity.

The critical difference between the present and prior studies is the finding of an overlap between regions activated for procedural and declarative learning. In contrast to earlier stud-

ies (Grafton et al. 1995; Hazeltine et al. 1997; Honda et al. 1998; Rauch et al. 1995), we 1) measured activation for procedural and declarative knowledge in alternation, rather than sequentially, precluding order and time effects; 2) compared procedural and declarative knowledge for the identical sequence; and 3) equated performance between the declaratively and procedurally learned sequences by using the explicit-covert condition. The explicit-covert condition allowed us to compare activation between conditions with equivalent RTs (implicit and explicit-covert), but different learning histories (implicit or explicit).

Comparing activation between different levels of performance is inherently problematic because activity may shift from certain regions to others as skill develops and performance improves. Neuroimaging of procedural learning has demonstrated such shifts with mirror reading (Poldrack et al. 1998), and with declarative learning, such as explicit sequence learning (Rauch et al. 1998; Sakai et al. 1998; Toni et al. 1998). In this study, the left inferior parietal cortex was active in the explicit-covert and implicit conditions but not in the explicit-overt condition. This difference between two identically trained explicit conditions must be due to the cessation of left inferior parietal activity in declarative learning before the end of training and prior to imaging. Taken together, these findings suggest that changes in performance levels (RTs) are associated with shifts in activation that are orthogonal to the procedural/declarative distinction.

Parietal cortex was activated in the SRTT, and the activation may be interpreted in terms of spatial attention. This region's importance in spatial attention has been well documented through lesion, electrophysiological, and functional neuroimaging studies (Corbetta 1998; Corbetta et al. 1993; Rafal 1994; Robinson et al. 1978). SRTT learning, in fact, has been shown to reflect the learning of a sequence of spatial response-locations rather than a sequence of movements (Willingham et al. 2000). The parietal cortex has also been specifically implicated in procedural sequence learning in a study of stroke patients who failed to learn the sequence following implicit instructions, even after extensive practice (Boyd and Winstein 2001). Although the lesion sites were somewhat heterogeneous, five of the eight patients' lesions included parietal cortex.

In this study, the region of left inferior parietal cortex that was associated with procedural learning showed an activation-performance correlation in each task. Faster subjects showed more activity in the region than slower subjects in each task, including the random. Because greater activation was associated with faster performance in the random condition, this correlation cannot reflect sequence learning per se. Instead, it must reflect processes operative in performance of the task. This activation also cannot be explained as a consequence of longer spatial attention in slower subjects, because those subjects had the least activation. Given the region's putative role in spatial attention, the correlation may reflect more focused attention to the visual display in faster subjects. More focused attention may result in faster orienting to the target once it appears, facilitating response time.

Left inferior parietal cortex was also more active in the implicit and explicit-covert conditions than in the explicit-overt or random conditions. In other words, this region showed the least activity in both the fastest and the slowest condition. In fact, our results suggested a diminution in left parietal activa-

tion from implicit to explicit-covert to explicit-overt. Activation in the explicit-overt condition was actually less than that in the random condition, but this result did not reach threshold. It is not clear why subjects would pay more attention to sequenced than random locations only when they were unaware of the sequence. It is difficult to reconcile this result with the general interpretation that this region mediates spatial attention to visual displays and is puzzling in light of the within-task correlation whereby faster subjects showed more activity. These findings suggest a more refined interpretation of the parietal cortex's role in spatial attention in this task. Spatial attention may facilitate orienting to targets in either an externally or internally driven fashion. In the implicit and explicit-covert conditions, orienting is externally driven by the appearance of the target. Greater activity in inferior parietal cortex in these conditions, compared with random, may reflect modulation from sequence-learning cortical or subcortical regions, a finding supported by the Boyd and Winstein (2001) lesion results indicating that parietal lesions are devastating to sequence learning. Feedback from these cortical and subcortical regions could increase parietal activation, and, in turn, sensitivity to the appearance of the targets. In the explicit-overt condition, however, subjects may consciously direct their attention to the location where they expect the target to appear. The explicit-overt condition, then, may involve less externally driven orienting than the other conditions, which could account for the relative reduction in activation in inferior parietal cortex.

Consciously or internally driven attention shifts may be supported by more superior parietal areas, which were active in the explicit-overt, but not the other conditions. Such a functional distinction between inferior and superior parietal regions is consistent with lesion research reporting impaired externally mediated orienting in patients with parietal lesions that included the temporal-parietal junction but not in patients with more superior lesions (Friedrich et al. 1998). It is also consistent with functional neuroimaging data. Consciously shifting attention to a predictable sequence of locations activates superior but not inferior parietal cortex (Corbetta et al. 1993). While Corbetta et al. also found that the inferior parietal cortex was active in a condition requiring externally driven attention shifts, their results fall short of the double dissociation reported here, because the superior region was also active in that condition. In contrast, we found that inferior parietal was more active in the implicit than the explicit-overt condition, and that superior parietal was more active in the explicit-overt than implicit condition.

Dorsal prefrontal cortex may mediate a function parallel to the conscious direction of attention, the conscious selection of responses. Activation levels in left dorsal prefrontal cortex correlated across subjects with how well they learned the explicit sequence. Subjects who showed the greatest reduction in response time relative to the random sequence showed the least activation in the region. This finding is consistent with reports of reduced frontal activation in well-learned compared with newly learned sequences, and under conditions of reduced attention due to the attainment of advanced levels of performance (Jenkins et al. 1994; Jueptner et al. 1997b). Activation in left dorsal prefrontal cortex also increases as subjects learn to categorize visual patterns (Seger et al. 2000). Together, these findings suggest that the function of left prefrontal cortex

in sequence learning may be characterized by the conscious selection of responses (Willingham 1998). Such conscious selection prior to the target's appearance may facilitate response times under explicit conditions. After enough practice, however, performance may become automated and no longer depend on conscious selection of action. Thus subjects with more automated and faster responses may perform less conscious selection, and this may diminish left frontal activation.

Modulation in dorsal prefrontal cortex seems to precede measurable changes in awareness. Although this region was most active in the explicit-overt condition, it was also more active in the implicit and explicit-covert conditions than the random condition. This activation may correspond to the conscious selection of isolated movements, without awareness of the reason for choosing that particular movement. In other words, a person may guess where the next target will appear and prepare to respond accordingly, but may not realize that their intuition is based on developing sequence knowledge. If so, such activation may represent the first step in the construction of a recognizable sequence. There is no doubt that the antecedents of declarative knowledge are acquired during procedural sequence learning: given enough repetitions, normal subjects become aware of the sequence. Studies capitalizing on this fact measure procedural and declarative learning in turn, giving periodic explicit memory tests to determine when procedural learning ends and declarative begins (Honda et al. 1998; Pascual-Leone et al. 1994). Such an experimental design highlights the dichotomous nature of distinctions between non-awareness and awareness. Logically, however, there must be some incremental gain in knowledge with repetition of a sequence that, on crossing some threshold, allows subjects to become aware of that sequence. Theoretically, awareness could also grow incrementally, but we were not able to detect awareness of the implicit sequence in the present study even with a very sensitive explicit memory test. Therefore it seems that activation in left prefrontal cortex may be a prerequisite to awareness, reflecting a gradual gain in sequence knowledge.

This interpretation of dorsal prefrontal activity also appears consistent with a transcranial magnetic stimulation (TMS) study (Robertson et al. 2001). Although earlier lesion (Gomez Belderrain et al. 1999) and TMS studies (Pascual-Leone et al. 1996) implicated the dorsal prefrontal cortex in procedural sequence learning, Robertson et al. (2001) showed that TMS only disrupts procedural sequence learning that uses spatial cues. If the stimuli are colored patches, learning proceeds normally. They conclude that dorsal prefrontal cortex does not contribute to procedural sequence learning, but rather to short-term retention of spatial information in working memory. This suggested role is consistent with our interpretation that the dorsal prefrontal cortex may be instrumental in the conscious selection of spatial targets for movement.

We have interpreted the greater activation observed in the explicit-overt condition as being associated with the explicit direction of motor sequencing performance. It may also be that this greater activation reflects a greater cognitive load in this condition. Although SRTT learning is minimally affected by cognitive load (Frensch et al. 1999), that may not be the case for all motor skill learning. For example, Verdolini-Marston and Balota (1994) reported a deficit in pursuit rotor learning when subjects adopted a conscious strategy suggested by the experimenter, relative to a no-instruction baseline; the slower

learning may have been due to a greater cognitive load in the strategy condition. On the other hand, Papka et al. (1995) reported that a secondary task may disrupt eyeblink conditioning, but not due to cognitive load. Rather, the disruption occurs due to competition for timing or motor planning mechanisms. In sum, the role of cognitive load in procedural learning is not yet clear, and may differ across different varieties of procedural knowledge such as motor skill, classification, and classical conditioning.

The present findings indicate that when awareness and performance are well controlled, modulation occurs in the same neural network for procedural learning whether that learning is or is not accompanied by declarative knowledge. Declarative learning, however, activates many additional brain regions. This conclusion suggests an integral role for the procedural system in some skills requiring physical practice regardless of whether learning occurs with or without declarative memory

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