Brief Communication

The Relevance of the Nature of Learned Associations for the Differentiation of Human Memory Systems

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In a previous functional magnetic resonance imaging (fMRI) study we demonstrated an involvement of the medial temporal lobe (MTL) during an implicit learning task. We concluded that the MTL was engaged because of the complex contingencies that were implicitly learned. In addition, the basal ganglia demonstrated effects of a paralleled proceduralization of fixed stimulus-response associations. In the present study we directly tested the hypothesis that the MTL activation depends upon implementing the complex regularity in task material, whereas activation of basal ganglia does not. Therefore, we rearranged task material such that it did not contain any complex regularity. The statistical comparison of behavioral and fMRI data between the materials allowed for isolating effects that were directly related to the implicit learning process regarding the complex regularity. The results showed a reliable difference of fMRI signal limited to the MTL, indicating a specific functional role of the MTL in implicit learning of complex contingencies. Furthermore, no difference of BOLD (Blood-Oxygenation Level Dependent) signal in the basal ganglia and cerebellum were detected, supporting the assumption of a functional involvement of the structures in proceduralization of simple stimulus-response associations but not in implicitly learning complex relations. We therefore conclude that the nature of the learned associations is relevant for determining the neuronal focus of learning, rather than the accompanying awareness.

In general, human learning and memory are divided into two systems, and this dissociation is based on the occurrence of awareness for the developed memory. Implicit learning is defined as the acquisition of knowledge in incidental learning situations that can be expressed in the behavior (e.g., procedural knowledge) but cannot be recalled verbally, as opposed to the explicit memory system, in which facts and events are stored and can be deliberately reported (Squire and Zola-Morgan 1991; Reber and Squire 1994). Explicit memory, which occurs with awareness, has been associated with the function of the medial temporal lobe (MTL) whereas implicit learning, which occurs without awareness, has been attributed to the basal ganglia and the cerebellum (Thompson and Kim 1996; Squire and Zola 1997; Gabrieli 1998; Poldrack et al. 2001).

However, recent studies suggested that the functional dissociation of the MTL and basal ganglia for learning is more dependent on the type of the associations that were learned than on the awareness for the material (Chun and Phelps 1999; Rose et al. 2002; Henke et al. 2003; Schendan et al. 2003). In a previous functional magnetic resonance imaging (fMRI) study (Rose et al. 2002), we showed the relevance of MTL structures for the learning of complex contingencies, although the process was reliably implicit; that is, no conscious memory for the learned relations was reported. In the “number reduction task” (NRT), participants had to process an eight-digit string in each trial (Fig. 1). All strings were composed of the digits 1, 4, and 9. Participants were instructed to process the strings pairwise from the left to right by two given rules. The first rule, the “Same rule,” states that the result of two identical digits is the digit itself (e.g., 4, 4 results in 4). The second rule, the “Different rule,” states that the result of two nonidentical digits is the remaining third digit (e.g., 4, 1

results in 9). The practice of the explicit given Same-Different rules can be regarded as a proceduralization of fixed stimulus-response associations and resulted in a general decrease of reaction times (RTs). This procedural learning was accompanied by an increase in BOLD signal in the basal ganglia and the cerebellum. To establish a parallel implicit learning process for more complex contingencies, we embedded a “hidden rule” in the sequence of responses in each trial. Irrespective of the stimulus pattern, the response pattern in all trials followed the same underlying structure: the responses for the last three input positions were always the mirror image of the responses for the previous three input positions (Fig. 1: ... 9 1 4 4 1 9). Therefore, the last three responses (Half 2) were always determined by the responses for input positions 2, 3, and 4 (Half 1). The behavioral results clearly demonstrated that the abstract relations between the two input halves were learned in the absence of any explicit knowledge about the hidden rule. RTs decreased with learning, and this decrease was reliably larger for the determined inputs from Half 2 (Fig. 2A). This differential effect between input halves across learning was accompanied by BOLD signal changes in the superior parietal lobe (SPL) and in the MTL. The increase of BOLD signal in the MTL was strongly related to the implicit learning process, which was further demonstrated by correlating BOLD signal with RTs. With this experimental design we were thus able to dissociate the procedural learning of simple stimulus-response associations (basal ganglia and cerebellum) from implicitly learning more abstract contingencies (MTL).

The aims of the present study were (1) to directly test whether the MTL effect can be attributed to implicitly learning the hidden rule implemented in the regular task material, (2) to test whether the effect in the SPL can be also attributed to the implicit learning process or was related to an unspecific task effect, and (3) to determine whether the effect shown in the basal ganglia was independent of the implicit learning process but was related to the proceduralization of the Same-Different rules.

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Figure 1 The number reduction task (NRT). Examples of an NRT trial used in the previous study (A) and the present study (B). The hidden structure in the previous study ensured that the final three responses were determined by the previous three responses. The mirror symmetry of responses was learned in an implicit way. In the present study the identical material was rearranged to result in nondeterminant responses; that is, the final responses (Half 2) were not the mirrored responses from Half 1.

Therefore, we rearranged the task material from the previous study such that response strings contained the same stimulus-response associations (the explicit given processing rules) as in the last study, but no hidden rule. All other experimental parameters were kept identical in both studies to allow for a statistical between-group comparison. The between-group design (material with and without the hidden rule) was chosen to directly test for effects related to the presence of the hidden rule. We expected that the participants should again learn to apply the given stimulus-response associations resulting in procedural memory that should not differ from the regular material of the previous experiment. If basal ganglia are engaged in procedural learning of the processing rules regardless of the explicit nature of the associations, then activation of basal ganglia should not differ between task materials. In addition, if the MTL is relevant for implicitly learning the hidden rule, then we should find differences in MTL activity between the two task materials. However, this prediction is in contrast to other models suggesting a general role of the basal ganglia in implicit learning and MTL structures in explicit learning (Reber and Squire 1994). If indeed the basal ganglia contributed to the implicit learning of the abstract relations expressed by the hidden rule in the previous experiment, then we should find a reduced activation of basal ganglia in the present experiment. In the present experiment, the task material did not contain any hidden rule such that no constant relations can be learned in an implicit way besides the processing rules. In addition, if the MTL activation found in the previous study indicates a nonspecific effect that may be related to the tasks and not to implicit learning, then again we should find a reliable difference in BOLD signal in the MTL between the first and the second halves of the response sequence, and we should find no difference in the MTL between the two task materials.

RESULTS

Behavioral Results

In the postexperiment questionnaire, no participant reported the presence of an observed regularity or any awareness about the

regular double input that was present in each response string (see Methods section for details). The absence of explicit knowledge about the hidden rule was tested more extensively in the previous study (Rose et al. 2002). Accuracy was calculated for each participant as mean error rate per session. A one-way ANOVA indicated that participants reduced errors across sessions ($F(4,28) = 14.3$, $P < .001$). The comparison with the group of the previous study revealed no difference in error rate ($F(1,15) = 2.5$, ns). Mean RTs were calculated with respect to the appearance of the correct response for each single input and each session. A two-way ANOVA (factors position and session) revealed a general decrease of RTs across sessions ($F(4,28) = 13.0$, $P < .001$), demonstrating procedural learning of the processing rules. In the previous study, implicitly learning the hidden rule resulted in a decrease of RTs across sessions that was more prominent for the second half of inputs. This differential effect between input halves with learning as reflected by the interaction effect was used to characterize the implicit learning regarding the hidden rule in both the behavioral and fMRI data. In the present study, the identical interaction term was also reliable ($F(4,28) = 6.1$, $P < .05$). However, as can be seen from Figure 2B, it was due to exact the opposite modification with learning; that is, the difference between input halves decreased across sessions. Most importantly, the group comparison between the previous and present studies emphasizes this obvious difference (Fig. 2). As expressed by the three-way interaction term of group $\times$ session $\times$ input ($F(4,60) = 10.3$, $P < .001$), learning resulted in a much larger decrease of RTs for the second half of inputs only if the material contained the hidden rule (Fig. 2A).

Functional Neuroimaging

Procedural Learning of the Same-Different-Rules

For a comparison with the results from the previous study, we modeled each learning trial by two box-car functions for the first inputs 2–4 (Half 1) and the second responses 5–7 (Half 2). The procedural learning of the Same-Different rules was accompa-

Figure 2 Reaction times (RTs). Mean RTs for both studies separately for Half 1 (circles) and Half 2 (stars). The increasing difference between input halves with learning was restricted to the material with the hidden rule (A) and reflected the implicit learning process. For the unstructured material (B), the general decrease of RTs reflected the proceduralization of the Same–Different rules as in the structured material, but the difference between input halves did not increase with learning. Negative values were due to the fact that RTs were measured with respect to the appearance of the previous result, and with implicit learning the participants responded before the result appeared on the screen.

nied by a linear increase in BOLD signal across sessions for both Half 1 and Half 2 in the basal ganglia (Fig. 3) and the cerebellum (Table 1). The group analysis indicated an identical increase in BOLD signal across learning for the material with and without the hidden rule in the basal ganglia and the cerebellum. No difference between materials was obtained.

Effects of Input Half

In the previous study, the significant interaction of input-half (Half 1 vs. Half 2) with session indicated implicit learning of the hidden rule. With the decreasing RTs for Half 2, the BOLD signal in the MTL increased with learning for Half 2 but not for Half 1. For the material without the hidden rule, the identical interaction contrast was also estimated. As for the material with the hidden rule, without the rule, in parietal areas an interaction effect was also evident, reflecting mainly a decrease of BOLD signal for the inputs of Half 1 and no modification for Half 2 (Table 2). Most importantly, the interaction contrast for the material without the hidden rule revealed no effect within MTL structures across learning ($P < .05$ uncorrected). In the MTL, the BOLD signal was not modulated differentially for both input halves across sessions (Fig. 4). The difference in MTL activation between the material was documented by a group comparison of the interaction contrasts (therefore, a three-way interaction of half $\times$ session $\times$ material). The comparison between materials demonstrated that the fMRI signal increased across learning only

for the inputs that were determined by the hidden rule within MTL structures.

DISCUSSION

The behavioral data from the present study further support the assumption that the complex structure of responses generated by the hidden rule caused an implicit learning process. The present data confirmed that the RT increase for the second half of inputs is specific for the material with the hidden rule, because it was not detectable when no regularity was incorporated. Therefore the behavioral effect cannot be attributed to an unspecific position effect; that is, the responses were not simply faster because they were the final inputs. The small manipulation of rearranging the identical material resulted in a reliable difference of BOLD signal that is limited to the MTL. This is strongly indicative of a specific functional role of the MTL in implicitly learning the complex contingencies encoded in the hidden rule. Furthermore, a comparable increase of BOLD signal in the basal ganglia and cerebellum with both types of material supports the assumption of a functional involvement of these subcortical motor structures in the procedural learning of simple stimulus-response associations.

The group comparison revealed no difference for the increase of BOLD signal across sessions in the basal ganglia and the cerebellum between both types of material. Therefore,

Figure 3 Procedural learning. Effects of the proceduralization of the Same–Different rules in the present study within the basal ganglia and mean regression coefficients across the first five sessions separately for the inputs of Half 1 (circles) and Half 2 (stars). With the general decrease of RT, the BOLD signal in the basal ganglia increased across sessions. No difference between material was detected.

the implicit learning observed with the hidden rule did not result in an enhanced BOLD signal in these structures compared to the material without the hidden rule. This is in accord with our hypothesis that the functional role of the basal ganglia is restricted to procedural learning of the stimulus–response associations determined by the Same–Different rules, and that these structures are not involved in implicit learning of the hidden rule.

Possibly, the cerebellar involvement was related to the modification of performance, that is, the decrease of RT, and not

to learning per se, as was recently demonstrated in a serial reaction time task (SRTT), where a response sequence can be learned implicitly (Seidler et al. 2002).

The role of basal ganglia in learning stimulus–response associations was also demonstrated in other SRTT studies (Grafton et al. 1995; Rauch et al. 1995; Hazeltine et al. 1997; Peigneux et al. 2000). In contrast, basal ganglia were also reported to be active in the SRTT when the sequence was learned in an explicit way (Willingham et al. 2002; Schendan et al. 2003). In the latter studies, a large overlap between activations related to implicit and explicit learning was reported, although somewhat different subregions within the MTL and basal ganglia were involved in implicit and explicit learning. Further, it was demonstrated that the basal ganglia were also involved in learning probabilistic stimulus–response associations (Poldrack et al. 2001). In our present study, we were able to dissociate implicit learning of complex contingencies from the procedural learning of fixed stimulus–response associations. Implicitly learning the hidden rule did not affect activity in the basal ganglia. However, with both materials (with and without the hidden rule) the proceduralization of the Same–Different rule resulted in an increase of the BOLD signal in the basal ganglia, irrespective of input half (Half 1 and Half 2). Therefore, we can conclude that the involvement of the basal ganglia in learning is not determined by the presence of a hidden structure that resulted in implicit learning, but rather by learning simple stimulus–response associations. Thus, the functional role of the basal ganglia is more dependent on the type of associations that are learned than on the presence of an implicit learning process.

The relevance of the nature of the learned associations also applies to the function of the MTL in learning. The statistical comparison between the two studies shows that the BOLD signal increased across learning only for the inputs that were determined by the complex contingencies of the hidden rule. For the nondetermined inputs from Half 1 and for both halves of the present study without the hidden rule, no change over time or related to performance was detected in the MTL. Therefore, the results from the three-way interaction

of material with input half with session strongly suggests that the increase of activity in the MTL was not determined by the input position per se but was directly related to the presence of the hidden rule and the related implicit learning process.

On the other hand, with both materials an interaction effect between input half and session was found in the SPL, indicating an unspecific effect not related to learning. The known role of the parietal lobe in visual attention (Büchel et al. 1998; Kastner and Ungerleider 2000) suggests that the effect might be related to a decrease in the attentional demands with learning

Table 1. Effects of the Proceduralization of the Same Different Rules for Each Material

Coordinates (mm) and magnitudes of main activations for Proceduralization								
	t	x	y	z	t	x	y	z
	With hidden rule				Without hidden rule			
Right basal ganglia	10.83**	27	0	0	6.08**	21	18	−9
Left basal ganglia	5.08**	−21	0	0	10.54**	−18	−12	0
Right cerebellum	8.25**	21	−66	−30	7.49**	21	−78	−27
Left cerebellum	7.42**	−30	−60	−30	5.84**	−6	−75	−21
Group differences (increase × material)	no effects in ROIs							

The comparison between the materials (lower section) resulted in no reliable difference within basal ganglia or cerebellum. Results from the fMRI random effects analysis (** $P < .05$ corrected for multiple comparison with SVC (10 mm³)).

the Same-Different rules in Half 2 over time. Importantly, the comparison between materials restricted the effect of implicit learning of the complex contingencies of the hidden rule to the MTL.

This is in accord with previous data showing that the MTL acquires flexible, relational knowledge in explicit learning (Pol-drack et al. 2001). However, learning of the hidden rule did not result in conscious knowledge about the regularity and therefore can be termed implicit. This finding is in conflict with current theories linking the function of the MTL directly to conscious recollection of memories (Squire and Zola-Morgan 1991; Schacter 1997; Eldridge et al. 2000); that is, effects within the MTL should be limited to explicit memory. However, our findings of MTL effects for implicit learning are in accord with a recent study that demonstrated MTL activity during learning of an SRTT under both explicit and implicit conditions (Schendan et al. 2003). In another study, MTL activity was observed during the formation of new semantic associations without awareness (Henke et al. 2003), indicating that an explicit access to the memory is not a necessary outcome of the processing in MTL structures. The idea that the MTL may be necessary for explicit as well as for implicit memory is further supported by findings demonstrating impaired implicit learning in amnesic patients with lesions to the MTL (Chun and Phelps 1999).

It was postulated that the integration of spatiotemporal information and the encoding of event sequences are core functions of the MTL, relating its function to episodic memory by bridging temporal gaps between stimuli (Eichenbaum 1997, 2000). The encoding of spatiotemporal relations may also be relevant for extracting the complex sequential relations implemented by the hidden structure in the NRT. Our results strongly suggest that the MTL structures are involved in the formation of complex associations that cannot be expressed as simple stimulus-response associations. One may speculate that complex associations most often occur when the learned memory is explicit, that is, consciously available. This might be the reason why MTL involvement has been exclusively linked to explicit memory processing. With our paradigm, we dissociated the two processes and unequivocally demonstrated that the formation of complex associations is the relevant function that determines MTL involvement.

MATERIALS AND METHODS

Participants

Eight healthy volunteers (mean age 23 yrs, range 22–26 yrs, 5 females) performed the number reduction task (NRT) without the hidden rule, and 10 healthy subjects (mean age 26 yrs, range 22–39 yrs, 5 females) participated in the previous study with the

Table 2. Effects of the Interaction Contrast of Input Half × Session That Represented the Implicit Learning for the Structured Material Separately for Each Material

Coordinates (mm) and magnitudes of main activations for effect of Input half × session								
	t	x	y	z	t	x	y	z
	With hidden rule				Without hidden rule			
Right superior parietal	6.35**	12	−66	63	6.86**	6	−72	45
Left superior parietal	6.09**	−12	−66	57	6.25**	−15	−75	54
Right MTL	4.84**	39	−18	−21	No effect			
Left MTL	4.43**	−39	−15	−24	No effect			
Group differences (input half × session × material)								
Right MTL (subiculum)	2.62*	18	−30	−9				
Right MTL (parahippocampus)	2.26*	36	−30	−21				
Left MTL	1.99*	−15	−39	−9				

The comparison of these interaction contrasts resulted in a difference limited to MTL structures (lower section). Results from the fMRI random effects analysis (* $P < .05$; ** $P < .05$ corrected for multiple comparison with SVC (10 mm³)).

Effects within MTL:

Figure 4 MTL effects. Result of the three-way interaction of material $\times$ input half $\times$ sessions (upper section) and mean regression coefficients across the first five sessions within the MTL (lower section, at $x = 39$, $y = -18$, $z = -21$). Only for the determined inputs from the structured material was an increase of BOLD signal in relation to the implicit learning observed (right lower panel). In the material without the hidden structure, no modulation across sessions was detected in MTL structures (left lower panels).

material including the hidden rule (Rose et al. 2002). All subjects were right-handed, and had normal or corrected-to-normal vision. The study was approved by the local ethics committee, and all participants gave written informed consent prior to participating in the study.

Materials

Stimuli were presented in white on a gray background. Stimulus sequencing was controlled by a PC that ensured synchronization with the MR scanner using the software program Presentations (<http://www.neurobehavioralsystems.com>). An LCD projector projected the stimuli on a screen positioned on top of the head coil, which was viewed by the subjects through a mirror ($10 \times 15^\circ$ field of view). Participants entered the responses by pressing buttons on an MR-compatible device.

Procedure

Participants saw a string of eight digits on the screen (Fig. 1). All strings were composed of three different digits (1, 4, and 9). Par-

ticipants were asked to process the stimuli pairwise from the left to the right by applying the Same-Different rules. The Same rule states that two identical digits require the subject to respond with the digit itself (i.e., 4, 4 results in 4). The Different rule states that two different digits require responding with the remaining third digit (i.e., 1, 4 results in 9). First, the two left-most digits of a given string are processed (in the example in Fig. 1, the digits 1 and 9). According to the Different rule, two different digits require responding with the remaining digit; the first pair provided 4 as the result. After 1.6 sec, the correct result was displayed below the third digit. The task of the participants was to respond before the result appeared, however. All remaining comparisons were then made between the preceding result and the next digit in the digit sequence; that is, the result of the first comparison, 4, was compared with the digit 1, which was the next digit in the digit sequence (position three). The result of this comparison is, according to the Different rule, the digit 9. Next, this result (i.e., the digit 9) was to be compared to the next digit in the string, a 4. Comparing the digits 9 and 4, again according to the Different rule, results in a 1. On any given trial, participants generated and

entered a total of seven responses. The application of the Same-Different rules was identical in both studies and should result in procedural memory with learning.

In the previous study, we incorporated a structural invariant in every response string. Overall, 54 eight-digit strings were constructed with a hidden rule in the response pattern of the form “x a b c b a” (x, a, b, and c representing the digits 1, 4, or 9). Thus, the last three responses were always the mirrored repetition of the responses at positions 2–4. It is important to note that the regularity in the response pattern does not correspond with any overt structure in the presented stimulus string. For example, the digit strings 1 4 1 9 4 9 4 9 and 1 4 4 4 1 4 4 both result in a response string that followed the hidden rule (i.e., 9 4 1 9 9 1 4 and 9 1 9 1 1 9 1), but do not share any other structural characteristic. An important feature is that due to the hidden rule, in each trial the first half of inputs is not determined, whereas the second half of inputs can be predicted by previous responses. The participants received no information about the principle underlying the construction of the strings.

In the present study the same material was rearranged to form new strings without the hidden rule. In this new material, the last responses were not determined by previous inputs, but the response strings matched the other characteristics of the original material. The number of Same and Different rule applications and the digits used as final results were identical in both studies. As in the structured material, a repeated input was incorporated in each response string, but at variable locations. In addition, all experimental conditions such as the instruction and training remained constant across both studies. Therefore the only difference between both studies concerns the presence or absence of the hidden rule that determined the last input half in the previous study.

For the material with the hidden rule, we ensured the absence of explicit knowledge and excluded one participant who demonstrated explicit memory regarding the hidden rule. For the new material in the present study, the participants only had to rate the presence of a regularity and were asked whether they noticed that in each trial there was a double input.

Design

Each trial consisted of the processing of an eight-digit string which required the calculation of seven responses. As in the previous study, the time limit for each input was 1.6 sec, resulting in a trial duration of 11.2 sec (7×1.6). The length of the intertrial interval (ITI) with a fixation cross on the screen was randomized between 2 and 10 sec and served as a baseline condition. For each of the first five sessions, 30 digit strings were randomly chosen from the list with the material without the hidden rule (duration about 9 min per session). Each session was followed by a rest period of 5 min.

fMRI Methods

The fMRI parameters remained identical to allow a direct statistical comparison of the fMRI data between the material with and without the hidden rule. Functional MRI was performed on a 1.5T system (Siemens Vision) with a gradient-echo EPI T_2^* sensitive sequence in 32 contiguous axial slices (3-mm thickness with 1-mm gap, TR 2.6 sec, TE 40 msec, flip angle 90° , field of view 210×210 mm², matrix 64×64). For display purposes, a high-resolution ($1 \times 1 \times 1$ mm voxel size) structural MRI was acquired for each participant using a standard 3-D T_1 -weighted FLASH sequence.

Image processing and statistical analysis were carried out using SPM99 (<http://www.fil.ion.ucl.ac.uk/spm>). All volumes were realigned to the first volume, spatially normalized to a standard EPI template (SPM99), and smoothed using a 10-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. As in the previous study, the data analysis was performed by modeling the first half of responses and the second half as box-car functions with variable duration convolved with a hemodynamic response function (HRF). The duration was computed by the indi-

vidual processing times for the first and the second halves of inputs for each trial. Therefore, the block of activation evoked from the processing of one trial (processing of one complete eight-digit string) was subdivided in the first half of inputs, and the second half and both subblocks were modeled as separate regressors. It should be noted that differences between Half 1 and Half 2 are confounded by experimentally dictated differences between those two conditions, and therefore a direct comparison between input halves yielded no reliable information. This was acceptable because learning was always reflected by an interaction of input half with session (and with material) and because we did not analyze categorical differences between input halves. An additional regressor was created for the error trials modeling the whole trial as a regressor with fixed duration (11 sec). Regression coefficients for all regressors were estimated using least-squares within SPM99 (Friston et al. 1995). A high-pass filter with a cut-off period of 120 sec and a low-pass filter (Gaussian envelop FWHM of 4 sec) were used.

Two contrasts were estimated for each subject of each group (with and without the hidden rule). First, in the previous study, implicit learning was reflected by the interaction of session and input half. The identical linear interaction contrasts were estimated for the present study. Second, to assess the procedural learning of the Same-Different rules, a contrast modeling an increase for the first and second halves of each trial was estimated in both groups. Second-level analyses were performed independently for each group and as a between-group comparison.

For the between-group analysis, a second-level analysis was performed, treating intersubject variability as a random effect. The results reflect the three-way interaction effects of session with input half with group. The threshold adopted was $P < 0.05$.

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