



Amnesic patients have residual prospective memory capacities

Beat Meier^a , Severin Fanger^a, Giannina Toller^a, Sibylle Matter^a, René Müri^{b,c}  and Klemens Gutbrod^{b,c}

^aInstitute of Psychology, University of Bern, Bern, Switzerland; ^bDepartment of Neurology, University of Bern, Bern, Switzerland; ^cDepartment of Cognitive and Restorative Neurology, Bern University Hospital, Bern, Switzerland

ABSTRACT

Objective: To investigate, in two separate studies, whether amnesic patients with a severe memory impairment can learn to perform a habitual prospective memory task when they receive immediate feedback on prospective memory failures (Study 1) and whether amnesic patients are able to benefit from previous habitual prospective memory performance after a 24-h retention interval.

Method: A prospective memory task was embedded in a lexical decision task (Study 1) and in a perceptual discrimination task (Study 2). Performance was compared across test halves. Participants received immediate performance feedback on prospective memory failures that served as a reminder for the prospective memory task. A retest was performed after 24 h in Study 2, but without immediate feedback in the first test half. **Results:** In Study 1, amnesic patients performed at a lower level than the control group, but they improved significantly across the experiment. In Study 2, the results of the first session replicated this pattern. The results of the second session showed a performance breakdown in amnesic patients. However, one single reminder was enough to boost performance again on the level of the second part of day one. **Conclusions:** This indicates that amnesic patients have residual prospective memory capacities and that providing immediate feedback is a promising strategy to draw on these capacities.

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Amnesia refers to a profound impairment in episodic memory. Amnesic patients have only very limited capacity to remember experiences from their past, they are impaired on conventional memory tests, and severely disabled in their daily lives. However, as some forms of learning and memory are spared, amnesia is a selective memory deficit. Particularly, implicit memory, that is, the capacity to benefit from previous learning episodes (Gabrieli et al., 1994; Graf & Schacter, 1985; Graf, Squire, & Mandler, 1984; Meier, Theiler-Bürgi, & Perrig, 2009; Milner, Corkin, & Teuber, 1968), implicit learning, that is, the capacity to draw from regularities in the environment (Curran, 1997; Meier, Weiermann et al., 2013; Nissen & Bullemer, 1987; Vandenberghe, Schmidt, Fery, & Cleeremans, 2006), as well as other forms

CONTACT Beat Meier  beat.meier@psy.unibe.ch

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of procedural skill and habit learning are still functional (Cohen & Squire, 1980; Schmidtke, Handschu, & Vollmer, 1996). The goal of the present study was to test whether amnesic patients would be able to learn to perform a habitual prospective memory task.

Prospective memory is the ability to remember to perform a previously formed intention at the appropriate occasion. It is highly relevant in everyday life and is involved in tasks such as remembering to buy groceries on the way home from work, to keep an appointment or to comply with a medication prescription regimen. Prospective memory tasks can be classified as episodic when they are concerned with one-time events and they can be classified as habitual when they need to be executed repeatedly (cf., Cuttler & Graf, 2009; Einstein, McDaniel, Smith, & Shaw, 1998; Elvevåg, Maylor, & Gilbert, 2003; Matter & Meier, 2008; Meacham & Leiman, 1982; Meacham & Singer, 1977; Meier, Matter, Baumann, Walter, & Koenig, 2014; Vedhara et al., 2004). Complying with a medication prescription regimen can be considered as a typical habitual prospective memory task. Importantly, failures of habitual prospective memory often have immediate consequences (e.g. worsening health) and thus provide immediate feedback. In the present study, we modeled this particular characteristic by providing feedback in the course of the acquisition of a habitual prospective memory task. As previous research has shown that amnesic patients are able to learn from immediate feedback (Foerde, Race, Verfaellie, & Shohamy, 2013; Knowlton, Squire, & Gluck, 1994), we considered this as a promising strategy to boost prospective memory performance in amnesic patients.

So far, only few studies have addressed prospective memory in amnesic patients, and they have all used episodic rather than habitual event-based tasks. Carlesimo, Lombardi, and Caltagirone (2011) investigated two patients with thalamic amnesia. Both of them performed poorly on the prospective memory task. However, a closer analysis revealed that one of the patients did not remember the target words, while the other was not able to activate the intention despite being able to recall them. This illustrates the complexity of a prospective memory task that typically involves two components: remembering *that* something has to be done (the prospective component) and remembering *what* has to be done (the retrospective component; cf. Cohen, Dixon, Lindsay, & Masson, 2003; Einstein & McDaniel, 1990; Meier & Zimmermann, 2015; Zimmermann & Meier, 2006). It is thus particularly important to keep the retrospective component as simple as possible. In a study that investigated patients with various etiologies, for example, Kopp and Thöne-Otto (2003) had to exclude patients with severe anterograde amnesia from their prospective memory study because they were not able to remember the prospective memory task at all.

Other studies have investigated prospective memory in patients with Korsakoff's syndrome who typically suffer from severe memory impairment. Brunfaut, Vanoverberghe, and d'Ydewalle (2000) found that despite large impairments in both executive functions and retrospective memory, prospective memory performance was surprisingly preserved, in particular when the processing requirements for the ongoing task and the prospective memory task were similar (cf. Meier & Graf, 2000). However, it is noteworthy that in this study, 8 prospective memory targets occurred within 22 ongoing task trials. Therefore, it is likely that the task rather recruited working memory processes than prospective memory retrieval. In a similar study, Altgassen, Ariese, Wester, and Kessels (2016) found that salient prospective memory targets improved performance in another group of patients with Korsakoff's syndrome, but not in a control group of alcoholics. In this study, 5 prospective memory targets occurred within 40 ongoing task trials. Thus, this setup may also have primarily made demands on working memory rather than proper prospective memory retrieval. Nevertheless,

all these studies suggest that under some circumstances prospective memory performance of patients with severe retrospective memory impairments may be somewhat spared (see also Umeda, Nagumo, & Kato, 2006, for encouraging results of training prospective memory in two patients with severe anterograde amnesic syndrome).

In the present project, we were interested in habitual, event-based, prospective memory performance. In particular, we investigated whether amnesic patients would be able to learn to perform a prospective memory task with repeated feedback. Compared to previous studies, the interval between prospective memory targets was enhanced to ensure proper prospective memory retrieval (cf., Graf & Utzl, 2001; Meier & Graf, 2000). To accomplish this, on average 30 ongoing task trials occurred between 2 subsequent prospective memory targets. In Study 1, we embedded a prospective memory task into an ongoing lexical decision task. The prospective memory task was simply to interrupt the prospective memory task (prospective component) and to press a particular key on the keyboard (retrospective component), thus keeping both prospective and retrospective memory load minimal. We expected that despite their profound retrospective memory impairment, amnesic patients would be able to learn the habitual prospective memory task. In particular, we expected that the patients would be able to benefit from feedback through repeated associative learning and from subsequently performing the appropriate action (cf., Foerde et al., 2013; Hainselin et al., 2014; Mimura et al., 1998). We suspected that this form of learning may be possible via intact brain systems, most likely the basal ganglia and related structures, similar to the spared performance in some implicit memory and procedural learning tasks (Curran, 1997; Knowlton et al., 1994; Nissen & Bullemer, 1987; Schmidtke et al., 1996).

We were also interested in the long-term consequences of these potential learning effects. Toward this goal, we used a similar setup in Study 2, but we retested the participants after a 24-hour retention interval. Importantly, no reminder of the prospective memory task was given at the beginning of the second session, and for the first half of the second session no feedback was given on failed prospective memory trials. Only for the second half, feedback was given. This allowed testing for potential habitual prospective memory consolidation effects. It is noteworthy that the few studies on prospective memory consolidation have found a performance benefit after a night of sleep (Diekelmann, Wilhelm, Wagner, & Born, 2013a, 2013b; Scullin & McDaniel, 2010). It has been suggested that sleep strengthens the prospective memory trace and particularly the association between cue and intention. This strengthening facilitates the automatic activation of the prospective memory response (Diekelmann et al., 2013a). Thus, in Study 2, we were specifically interested whether amnesic patients would be able to retain the prospective memory task after a 24-h retention interval that included a night of sleep in a similar way as non-amnesic control participants. As habitual prospective memory tasks are generally cued by specific target events in everyday life, for the sake of ecological validity we used specific target events in both studies (cf. Dismukes, 2008; Meacham & Leiman, 1982).

General method

Participants

Patients were recruited from the Department of Neurology at the Bern University Hospital. All of them had German as their first language. Inclusion criterion was the presence of a severe, circumscribed, and chronic memory impairment (time since onset >3 months) with

Table 1. Demographic and patient characteristics.

Patient ID	Study 1	Study 2	Age (years) Study 1	Age (years) Study 2	Education (years)	Sex	Etiology	Time since onset (months)
1	x	x	46	48	13	F	Herpes encephalitis	136
2	x	x	59	61	18	M	Hemorrhage	70
3	x	x	42	44	12	F	Hypoxia	63
4	x	x	57	59	19	M	Herpes encephalitis	82
5	x	x	40	42	16	M	Hemorrhage	91
6	x	x	53	55	13	M	Hemorrhage	150
7	x	x	43	45	13	M	Hypoxia	216
8	x	x	68	70	15	M	Infarction	218
9	x	x	58	60	19	M	Hemorrhage	152
10	x		58		17	M	Infarction	167
11	x	x	51	53	13	M	Hemorrhage	8
12	x	x	52	54	11	M	Hemorrhage	11
13	x		58		12	M	Hypoxia	5
14	x		22		11	M	Infarction	5
15	x		39		17	M	Hypoxia	Birth
16		x		60	17	M	Hypoxia	5
17		x		45	12	M	Herpes encephalitis	6
18		x		61	15	M	Infarction	8
Mean AP Study 1 (N = 15)		49.7 ± 11.3		14.6 ± 2.9	13 M 2 F			
Mean CG Study 1 (N = 15)		50.3 ± 11.8		15.0 ± 2.2	12 M 3 F			
Mean AP Study 2 (N = 14)			54.1 ± 8.3	15.0 ± 2.7	12 M 2 F			
Mean CG Study 2 (N = 14)			55.1 ± 8.3	15.7 ± 3.0	11 M 3 F			

Note: x = participated in the study; F = female; M = male; AP = Amnesic Patients; CG = Control Group.

normal intellectual functioning (cf. Aggleton, 2008). In total, 18 severely amnesic patients participated in this project, 15 in Study 1 (mean age 49.7 years; mean education 14.6 years), and 14 in Study 2 (mean age 54.1 years; mean education 15 years). Table 1 provides an overview of the demographic characteristics, the etiology, and time since onset. They have already participated in earlier studies and detailed descriptions of the lesions can be found there (Duss et al., 2014; Gutbrod et al., 2006; Meier, Rey-Mermet, Woodward, Muri, & Gutbrod, 2013; Meier, Weiermann et al., 2013). Five patients had damage mainly to the basal forebrain following a bleeding from a ruptured aneurysm of the anterior communicating artery (2, 6, 9, 11, 12). Three patients had damage mainly to the hippocampus bilaterally following herpes encephalitis (1, 4, 17). In one of these patients, also the basal forebrain was involved. Five

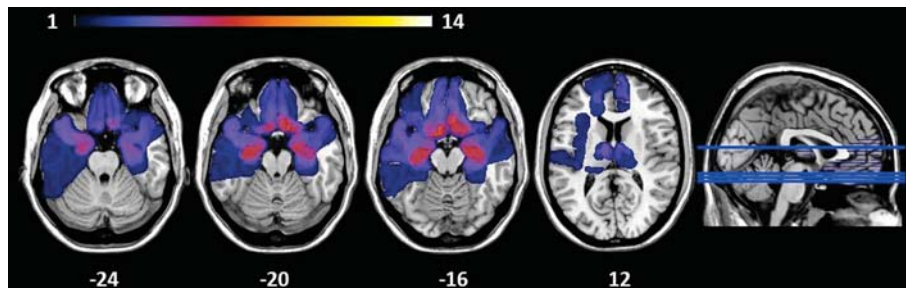


Figure 1. Brain maps showing the region of highest lesion overlap for the amnesic group.
 Notes: Lesions were drawn on templates with Z-values -24 , -20 , -16 , and 12 in Talairach space (Talairach & Tournoux, 1988). The color scale indicates the number of shared lesions for each brain area.

patients showed amnesia following an episode of hypoxia due to cardiac arrest (3, 7, 13, 16) or a complication during birth (15, i.e. this patient suffered from a developmental amnesia). Although magnetic resonance imaging (MRI) did not reveal any visible brain damage in these hypoxic patients, they were included in the study since hypoxia is known to cause primarily damage to the hippocampus (cf. Di Paola et al., 2008; Gold & Squire, 2006; Zola-Morgan, Squire, & Amaral, 1986). In the patient with developmental amnesia, a volumetric analyses revealed an isolated atrophy of 40% of the hippocampus bilateral. Four other patients had suffered thalamic infarction (8, 10, 14, 18). One patient (5) became amnesic following bleeding from an aneurysm of the right middle cerebral artery.

Lesions were traced from the latest available magnetic resonance or computer tomography imaging (two cases) onto the Standard Neurological Institute (MNI) brain separately for each patient using MRICron (Rorden & Brett, 2000). The lesions of the four hypoxic patients were not included because no damage was visible on MRI. In this way, all the lesions were in the same normalized Talairach space. Of the available images, a lesion overlap image for the whole group was performed also using MRICron. Figure 1 shows this overlap image of brain lesions. It is apparent from Figure 1 that the lesions of all the remaining patients comprised memory-critical structures such as the basal forebrain, the hippocampus, and the anterior thalamus. As shown in Table 2, there was a dissociation between normal IQ and severe memory deficits in the group of amnesic patients.

Control groups consisted of 15 (Study 1) and 14 (Study 2) healthy participants. They were recruited by word of mouth such that they were matched to an individual patient with regard to age (\pm one year), years of education (\pm two years), and gender (as possible). Study 2 was conducted about two years after Study 1. The project was approved by the local ethics committee, and all participants agreed to take part by giving written informed consent.

Study 1

Method

Materials

For the lexical decision task, a total of 145 high-frequency nouns (no proper names, no furniture) with a length of 4 to 9 letters were selected from the CELEX database (Baayen, Piepenbrock, & Gulikers, 1995). For each word, a non-word was generated by keeping the

Table 2. Neuropsychological results of amnesic patients: intelligence and verbal memory.

Patient ID	Study 1	Study 2	IQ	Memory		
				Learning (total trials)	Delayed recall	Recognition (Hits-FA)
1	x	x	94 ^a (34)	26 (<1)	0 (<1)	-2 (<1)
2	x	x	119 ^a (90)	27 (<1)	0 (<1)	8 (3)
3	x	x	89 ^a (23)	30 (<1)	0 (<1)	-5 (<1)
4	x	x	118 ^a (88)	30 (<1)	0 (<1)	-6 (<1)
5	x	x	128 ^a (97)	29 (<1)	1 (<1)	6 (1)
6	x	x	126 ^a (96)	30 (<1)	3 (<1)	-4 (<1)
7	x	x	102 ^a (55)	36 (4)	1 (<1)	-6 (<1)
8	x	x	115 ^a (84)	24 (<1)	0 (<1)	0 (<1)
9	x	x	128 ^b (97)	30 (<1)	0 (<1)	9 (<1)
10	x	x	115 ^b (84)	33 (<1)	0 (<1)	2 (<1)
11	x		85 ^b (16)	37 (8)	5 (3)	-1 (<1)
12	x	x	85 ^b (16)	25 (<1)	1 (<1)	1 (<1)
13	x		95 ^b (37)	28 (<1)	3 (<1)	-1 (1)
14	x		97 ^b (42)	23 (<1)	1 (<1)	0 (<1)
15	x		128 ^b (97)	37 (2)	1 (<1)	8 (2)
16		x	108 ^b (70)	30 (<1)	2 (<1)	0 (<1)
17		x	100 ^a (50)	31 (<1)	2 (<1)	-1 (<1)
18		x	92 ^b (30)	25 (<1)	1 (<1)	3 (<1)
Mean Study 1			109.8 ± 17.4	29.6 ± 4.3	1.1 ± 1.4	0.6 ± 4.9
Mean Study 2			108.5 ± 14.4	29.0 ± 3.2	0.8 ± 0.9	0.4 ± 4.7

Notes: IQ was assessed either with ^aWechsler Adult Intelligence Scale (WAIS, Tewes (1991) or ^bMehrfachwahl-Wortschatztest (MWT, a German equivalent of the North American Adult Reading Test; Lehrl, Merz, Burkhard, & Fischer, 1991). Both tests are standardized with a population mean of 100, and a standard deviation of 15. Memory was assessed with the German version of the Rey Auditory Verbal Learning Test (RAVLT; Helmstaedter, Lendt, & Lux, 2001). The scores represent raw scores with age-, sex-, and education adjusted percentiles in parenthesis.

position of the first and the last letter while randomly changing the position of the middle letters, resulting in a pool of 290 stimuli for the lexical decision task. In addition, the word 'Tisch' (German for 'table') was used as the prospective memory target, which occurred 10 times across the experiment. Materials were arranged such that 20 to 40 lexical decision task items occurred between each prospective memory task occurrence.

Stimuli were presented in uppercase and in 18-point black Courier font against a white background in the center of the screen. The experiment was controlled by E-Prime 1.2 software (Psychology Software Tools, www.pstnet.com) running on an IBM-compatible computer with a 15" VGA monitor.

Procedure

For the lexical decision task, participants were informed that they would see a letter string on the computers screen and for each one they had to decide whether it was a word or a non-word by pressing the 'B'-key with the right index finger for a word and the 'N'-key with the right middle finger for a non-word. In addition, they were informed that an additional goal of the study was to investigate how well they would remember to carry out an intended activity in the future. Thus, for the prospective memory task, they were asked to press the '1'-key on the computer keyboard whenever the word 'Tisch' was presented.

A lexical decision task trial started with the presentation of an empty screen for 500 ms. Then, a letter-string was presented on the screen until a response was given. When a participant forgot to press the '1'-key for a prospective memory target trial, a message appeared on the screen to remind the participant of the prospective memory task. Specifically,

participants were informed that the word 'Tisch' had occurred and that their task was to remember to press the '1'-key on the keyboard for the word 'Tisch'. They were instructed to press the '1'-key to continue the experiment. This procedure was used to give immediate feedback for missed prospective memory responses and to make sure that the task became habitual. The whole experiment lasted approximately 20 min.

Results

Prospective memory task

Prospective memory performance was measured as correct responses to the target word. The results are presented in Figure 2. A mixed two-way analysis of variance (ANOVA) with the between-subject factor group (amnesic patients vs. control group) and the within-subject factor half (first vs. second half) gave a main effect of half $F(1, 28) = 4.699, p < .05$, with better performance in the second than in the first half. The main effect of group was marginally significant, $F(1, 28) = 3.78, p = .062$, illustrating the somewhat better performance of the control group compared to the amnesic patients. The group \times half interaction was not significant, $F(1, 28) = .38, p > .50$, suggesting that both groups showed the same benefit from repeated prospective memory task performance.

Ongoing task

Overall, proportion of correct ongoing lexical decision task responses was close to ceiling with .96 ($SE = .01$) for both amnesic patients and the control group and across halves, and was thus not further analyzed. For amnesic patients, lexical decision task reaction times (RTs) were 1390 ms and 1125 ms for the first and second half, respectively. For the control group, they were 1006 ms and 860 ms for the first and second half, respectively. A mixed two-factorial ANOVA with between-subject factor group (amnesic patients vs. control group) and within-subject factor half (first vs. second half) gave a main effect of group, $F(1, 28) = 5.78, p < .05$, half, $F(1, 28) = 58.01, p < .01$, and a significant group \times half interaction, $F(1, 28) = 4.92, p < .05$. The latter was due to the larger speed-up of amnesic patients compared to the control group in the second half of the experiment.

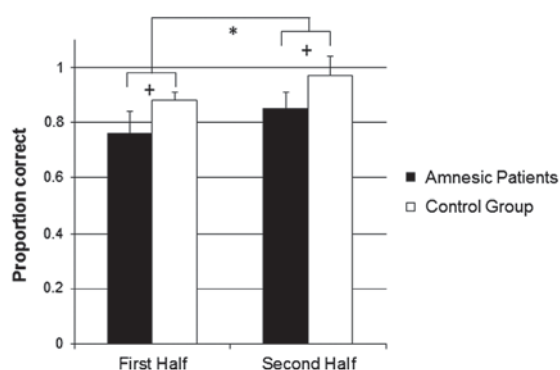


Figure 2. Study 1: Prospective memory performance, separate for first and second half and for amnesic patients and the control group ($N = 15$ in each group).

Notes: The asterisk refers to the main effect of test half ($p < .05$). The plus refers to the marginally significant effect of group ($p = .06$). Error bars represent standard errors.

Study 1 discussion

The purpose of Study 1 was to test whether severely amnesic patients are able to learn a habitual prospective memory task. We reasoned that by providing immediate feedback for prospective memory failures and thus by presenting context appropriate reminders, the patients may be able to learn the association between the prospective memory target and the intended action. This was indeed the case. Although performance of the amnesic patients was slightly lower than performance of the control group they reached a performance level of more than eighty percent correct responses in the second half of the experiment. Notably, performance of the control group also improved across the experiment and thus, it is reasonable to assume that the prospective memory task was indeed habitualized. This result is in line with a previous ERP-study in which we found that habitualization is a linear process also in the non-patient population (Meier et al., 2014).

The finding of above floor performance and continuous performance improvement in amnesic patients is a promising result for further investigation. Therefore, Study 2 was designed to test the impact of acquiring a habitual prospective memory response across a 24-h test interval. As performance of the control group approached ceiling in the second half of the experiment, we changed some features of the ongoing task and the prospective memory task. Specifically, in Study 2, we used a non-verbal perceptual discrimination task rather than a (verbal) lexical decision task, which has shown to be somewhat more difficult (cf. Meier et al., 2014). In this task, participants were presented with pairs of abstract colored fuzzy shapes and their task was to decide whether the two shapes are identical or not (cf. Zimmermann & Meier, 2006 for a similar approach). The prospective memory task was to give a different response for shapes that were presented in a specific color. That is, rather than using a specific prospective memory target word as in Study 1, we used a specific target color in Study 2.

Previous studies have reported beneficial effects of a 24-h interval including a night of sleep on episodic event-based prospective memory performance (Diekelmann et al., 2013a, 2013b; Scullin & McDaniel, 2010). Thus, the present study may also provide additional information on the effects of a delay of 24 h that included a night of sleep on habitual prospective memory. However, the main goal of Study 2 was – besides of replicating the results of Study 1 within the first session – to find out whether some of the learning effects of the amnesic patients transfer across a 24-h interval. Toward this goal, for the first half of the second session no feedback was given on failed prospective memory trials. This allowed testing for immediate long-term effects. Feedback was given for the second half of the trials. This allowed testing for weaker habitual prospective memory consolidation effects. Specifically, if amnesic patients have retained some habitual prospective memory knowledge, they should be able to reach their performance level of day one after fewer reminder feedbacks.

Study 2

Method

Materials

For a perceptual discrimination task, we selected fuzzy shapes from the materials of Slotnick and Schacter (2004). These consisted of 30 differently colored sets each with 20 different shapes. An additional set of white shapes was used for the prospective memory task. For

each color set, five identical and five non-identical shape-pairs were created. The materials were equally divided into two experimental sessions. Each session consisted of 300 different shapes in 30 different colors. A particular shape appeared twice in each block, once in an identical shape-pair and once in a non-identical shape-pair. For practice, 30 trials with 15 identical and 15 non-identical shape-pairs with 6 different colors were used. These were different from the shapes of the experimental blocks. The prospective memory targets were distributed at pseudo-randomized intervals of 20, 30, or 40 trials.

Procedure

The procedure of Study 2 was similar to Study 1. For the perceptual discrimination task, participants were informed that they will see a pair of shapes on the computer screen and that they have to decide whether the two shapes are identical or not by pressing the 'B' or the 'N'-key with the index finger and the middle finger of the right hand. For the prospective memory task, participants were instructed to press the '1'-key with their left index finger whenever a white shape-pair was presented.

A perceptual discrimination trial started with the presentation of an empty screen for 500 ms. Then, a pair of stimuli was presented, side by side horizontally arranged, against a black background, in the center of the screen. Each shape-pair was presented until a response was given. Then the shape-pair was removed and the next trial began. For missed prospective memory trials, immediate written feedback was given on the screen. Participants were informed that two white figures had occurred and that their task was to remember to press the '1'-key on the keyboard for white figures. They were instructed to press the 1-key to continue the experiment. Each session lasted approximately 20 min.

Session 2 took part exactly 24 h after session 1. Participants were only informed that they will perform the same task as yesterday, no mention of the prospective memory task was made. The procedure for the first and the second session was identical except that in session 2 no feedback was given for the first half of the trials. Feedback occurred only for the second half of session 2. For session 2, the stimuli for the practice trials were identical as in session 1.

Results

Prospective memory task

Prospective memory performance was measured as proportion of correct responses to the white target shapes. The results are presented in Figure 3. A mixed three-way ANOVA with the between-subjects factor group (amnesic patients vs. control group), and the within-subjects factors half (first vs. second half) and session (day 1 vs. day 2), gave a main effect of group, $F(1, 26) = 40.96, p < .01$, and a main effect of half, $F(1, 26) = 21.63, p < .01$, indicating better performance of the control group compared to the amnesic patients, and better performance in the second compared to the first half. However, this was qualified by both a two-way interaction group \times half, $F(1, 28) = 5.84, p < .05$ and a three-way interaction group \times half \times session, $F(1, 28) = 6.23, p < .05$.

To disentangle these interactions, further ANOVAs were performed separately for each session. For day 1, a two-way ANOVA with the factors group (amnesic patients vs. control group) and half (first vs. second half) gave a main effect of group, $F(1, 26) = 12.14, p < .01$, and of half, $F(1, 26) = 7.82, p = .01$, but no group \times half interaction, $F(1, 26) = .58, p > .45$. In

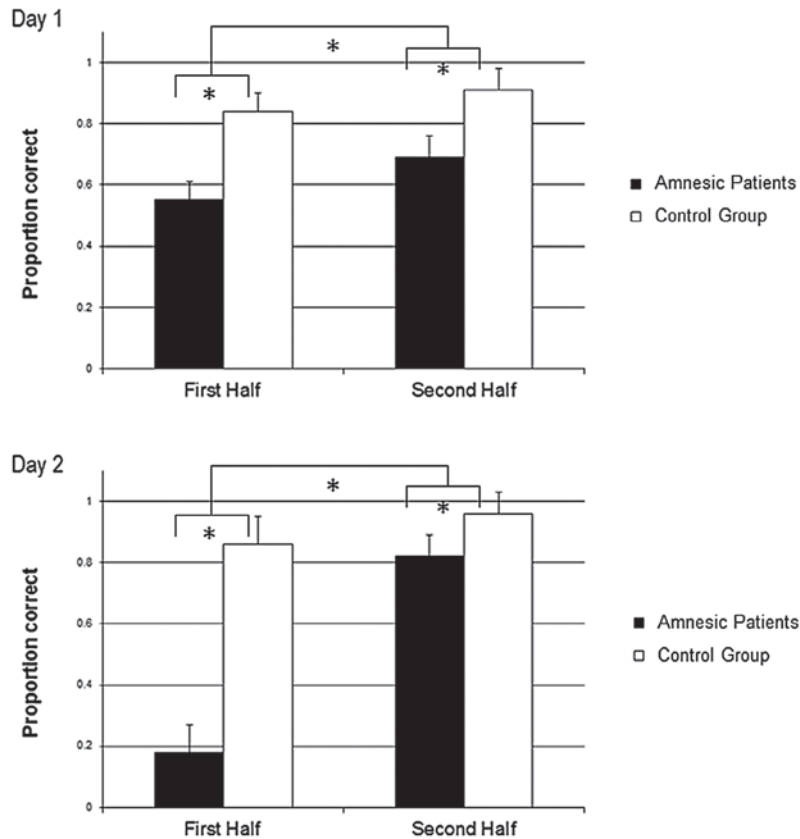


Figure 3. Study 2: Prospective memory performance, separate for first and second half and for amnesic patients and the control group ($N = 14$ in each group). Top: Day 1; Bottom: Day 2. No feedback was given in the first half of day 2.

Notes: Asterisks refer to the main effects of test half and group ($p < .05$). On day 2, these main effects were qualified by a significant interaction between test half and group ($p < .01$) due to the performance breakdown of amnesic patients in the first half. Error bars represent standard errors.

contrast, for day 2, the same two-way ANOVA gave a main effect of group, $F(1, 26) = 21.63$, $p < .01$, and of half, $F(1, 26) = 32.21$, $p = .01$, and also a significant group \times half interaction, $F(1, 26) = 16.43$, $p < .01$. This demonstrates a performance breakdown for the amnesic patients for the first half of day 2, when no feedback was given. Strikingly, however, a single feedback on day 2 was enough for the amnesic patients to boost performance to the same level as in the second half of day 1 (note that numerically performance was even higher in the second half of day 2 compared to the second half of day 1).

Ongoing task

Overall, the proportion of correct ongoing perceptual discrimination task responses was close to ceiling with .96 ($SE = .01$) for amnesic patients and .98 ($SE = .01$) for the control group and across halves on day 1, and with .97 ($SE = .01$) for amnesic patients and .98 ($SE = .01$) for the control group and across halves on day 2, and was thus not further analyzed.

For the amnesic patients, perceptual discrimination task RTs were 2300 ms and 2112 ms for the first and second half, respectively, on day 1, and 2208 ms and 2113 ms for the first

and second half, respectively, on day 2. For the control group, perceptual discrimination task RTs were 1759 ms and 1610 ms for the first and second half, respectively, on day 1, and 1500 ms and 1568 ms for the first and second half, respectively, on day 2. A mixed three-factorial ANOVA with the factors group (amnesic patients vs. control group), half (first vs. second half), and session (day 1 vs. day 2) revealed a significant day \times half interaction, $F(1,26) = 6.06$, $p < .05$, indicating an decrease in ongoing task RTs across halves on day 1, but not on day 2. However, no effects involving group reached significance. It is nevertheless noteworthy that in the group of amnesic patients in which prospective memory performance broke down in the first half of day 2, ongoing task RTs in the second half in which prospective memory performance recovered were numerically faster than in the first half. That is, there was no evidence that successful prospective memory performance was accompanied by a performance cost due to strategic monitoring for the target events (i.e. maintaining the intention in working memory).

Study 2 discussion

The purpose of Study 2 was to replicate the habitual prospective memory effects of Study 1 and to extend these findings across a 24-h interval. Using a different ongoing task (i.e. perceptual discrimination of fuzzy shapes) and different prospective memory targets (i.e. white shapes), the pattern of results of day 1 replicated Study 1. Compared to Study 1, performance was slightly lower as expected, in particular for the amnesic patients. These results replicate that with immediate feedback, even severely amnesic patients can learn a habitual prospective memory task.

The second purpose of Study 2 was to investigate prospective memory performance after a 24-h retention interval. Without being reminded about the prospective memory task, there was a performance breakdown in amnesic patients in the first half of day 2 in which no feedback was given on prospective memory failures. Nevertheless, performance was not completely at floor. Moreover, as soon as one single feedback was given as a reminder for the prospective memory task, performance of the amnesic patients improved remarkably and even reached a numerically higher level than in the second half of day 1. This indicates that amnesic patients possess some residual prospective memory capacities and a single reminder was enough to bring back the intention successfully.

It may be argued that at least some of this residual capacity may be due to the fact that most amnesic patients already took part in Study 1 and that they may have profited from this earlier experience. Although we consider this explanation as unlikely due to the long interval (i.e. about two years) between the two studies and the severe memory impairment of the amnesic patients, this argument would not invalidate our conclusions. In contrast, it would imply that amnesic patients are able to retain some relevant aspects of the association between a prospective memory target event and the required action even across a much longer interval.

Although we did not directly investigate the effect of sleep, the 24 h retention interval in Study 2 included a night of sleep, and thus, the results may also provide information on the effects of sleep on habitual prospective memory in a non-patient sample. In contrast to previous studies in which a performance increase was found when a prospective memory task was preceded by a night of sleep, we did not find a beneficial effect in the control group. There are several reasons for this result. First, it may be that due to the high performance on

day 1, performance was already close to ceiling and no further improvement was possible. Second, it may be that habitual prospective memory tasks show a different pattern of consolidation than episodic prospective memory task that were investigated in previous. This would suggest that habitual prospective memory tasks do not improve after a 24 h retention interval similar to some implicit learning tasks (cf. Meier & Cock, 2014). Third, it may be due to the fact that after the first session no specific instruction was given that the prospective memory task is still activated. In fact, a recent study has not found a beneficial effect of sleep neither for completed nor for reinstated prospective memory tasks (Barner, Seibold, Born, & Diekelmann, 2017). However, the present study was not set up to test the impact of sleep and there was no sleep-deprived control group as a comparison. Thus, the interpretation of this null-effect is rather speculative and needs further empirical investigation.

General discussion

Our results demonstrate that even severely amnesic patients are able to learn to perform a prospective memory task. In two studies, we found evidence that immediate feedback on prospective memory failures can enhance habitual prospective memory performance substantially. Moreover, the results of Study 2 suggest that even after a 24-h retention interval including sleep, some residual prospective memory capacity was still available in amnesic patients. Although the activation level of the residual representation was, on average, not sufficient to be triggered by the reinstated retrieval context in the first half of session 2, a single reminder feedback was sufficient to enhance the activation level of the intention representation to a comparable level as in the second half of session 2. This is a remarkable result with implications for a restorative rehabilitation approach for amnesic patients (cf. Raskin & Sohlberg, 2009).

However, one may argue that rather than being a consequence of acquiring a habitual prospective memory task, the intention was maintained in working memory between subsequent prospective memory target occurrences. We would like to emphasize that in order to reduce this possibility we have designed the tasks for this project such that the interval between prospective memory target events was purposefully longer than the typical range of working memory (i.e. 30 s). Given that between two subsequent prospective memory target events at least 20 ongoing task stimuli were presented, and that responding to each of these stimuli took on average more than one second (followed by a 500 ms inter-trial interval) in Experiment 1, and one second and a half (followed by a 500 ms inter-trial interval) in Experiment 2, even for the healthy control participants the interval between two subsequent stimuli was at least 30 s. As amnesic patients performed the ongoing task even slower, it is unlikely, that their performance was due to working memory maintenance of the intention. It is noteworthy that this methodological refinement contrasts previous studies.

We also used an empirical approach to further address the question whether keeping the prospective memory task in conscious awareness can explain the results of this study. As keeping an intention active is a resource demanding process, it typically comes with a cost in the ongoing task (cf. Smith, 2003). In Study 2, prospective memory performance of the amnesic patients was close to floor in the first half of day 2, that is, before feedback was given as a reminder. In contrast, ongoing task accuracy was at ceiling, thus ongoing task reaction times can be used as an index for the resources devoted to monitoring the prospective memory task unconfounded by a speed-accuracy trade-off. Thus, it was possible

to test whether performing the prospective memory task was costly by comparing ongoing task reaction times between first and second half (i.e. between a low vs. high prospective memory performance situation). This comparison revealed no reaction time differences between the two situations, and thus no evidence that a performance cost was associated with successful prospective memory performance. This finding indicates that successful prospective memory performance was rather a consequence of establishing an association between the target event and the required action than the consequence of monitoring induced by the feedback reminder. It seems that the strength of this association decreased across the 24-h interval, however, it was still strong enough to be reactivated by a single reminder. It is an avenue for further research to investigate whether repeated practice of the procedure implemented on day 2 of the present study can boost the strength of this association.

It is likely that the residual habitual prospective memory capacity of amnesic patients is based on learning the association between the prospective memory target events and the to-be-performed action, which is reinforced by immediate feedback in the case of failure. There is ample evidence that learning from feedback depends not on the medial temporal lobes or the basal forebrain (i.e. those structures typically implicated in severe anterograde amnesia) but rather on the neural substrates of the striatum (Foerde et al., 2013). This interpretation is line with findings of the spared capacity of amnesic patients in tasks involving implicit learning, implicit memory, and more generally, procedural learning.

An alternative and complementary view is that frontal areas are also involved in successful habitual prospective memory performance. There is ample evidence for the importance of the integrity of frontal areas both for planning and retrieving a prospective memory task (Burgess, Scott, & Frith, 2003; Landsiedel & Gilbert, 2015). Moreover, it has been suggested that spontaneous prospective memory retrieval processes are supported by a fronto-parietal network (Cona, Scarpazza, Sartori, Moscovitch, & Bisiacchi, 2015). This is consistent with source localization finds from an ERP-study in which habitual prospective memory performance was associated with increased parietal activation (Meier et al., 2014). Consistently, these brain areas are typically also intact in amnesic patients, in particular those who participated in the present study. Consequently, it is possible that habitual prospective memory depends on the integrity of both frontal and striatal systems.

Conclusion

To summarize, we present consistent findings that amnesic patient can learn to perform a habitual prospective memory task and that they preserve this capacity across a 24 h interval. This is a promising result both theoretically and for practical purposes. Theoretically, it provides evidence for the need to distinguish different types of prospective memory (i.e. habitual vs. episodic). It also indicates that the investigation of the effects of sleep on prospective memory performance is an important avenue for further research. Practically, more evidence is necessary to test whether these results can be generalized from a laboratory-based prospective memory task to naturalistic tasks and, more generally for which prospective memory tasks providing feedback is applicable as well in order to support amnesic patients in their everyday life.

Disclosure statement

The authors report no conflict of interest.

ORCID

Beat Meier  <http://orcid.org/0000-0003-3303-6854>

René Mürli  <http://orcid.org/0000-0001-6990-4188>

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