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Implicit task sequence learning in patients with Parkinson's disease, frontal lesions and amnesia: The critical role of fronto–striatal loops

Beat Meier [a,b,*], Brigitte Weiermann [a], Klemens Gutbrod [b,c], Marianne A. Stephan [c], Josephine Cock [a,b], René M. Müri [b,c], Alain Kaelin-Lang [c]

[a] Institute of Psychology, University of Bern, Fabrikstr. 8, 3012 Bern, Switzerland
[b] Center for Learning Memory and Cognition, University of Bern, Switzerland
[c] Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Switzerland

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ABSTRACT

The purpose of this study was to investigate the role of the fronto–striatal system for implicit task sequence learning. We tested performance of patients with compromised functioning of the fronto–striatal loops, that is, patients with Parkinson's disease and patients with lesions in the ventromedial or dorsolateral prefrontal cortex. We also tested amnesic patients with lesions either to the basal forebrain/orbitofrontal cortex or to thalamic/medio-temporal regions. We used a task sequence learning paradigm involving the presentation of a sequence of categorical binary-choice decision tasks. After several blocks of training, the sequence, hidden in the order of tasks, was replaced by a pseudo-random sequence. Learning (i.e., sensitivity to the ordering) was assessed by measuring whether this change disrupted performance. Although all the patients were able to perform the decision tasks quite easily, those with lesions to the fronto–striatal loops (i.e., patients with Parkinson's disease, with lesions in the ventromedial or dorsolateral prefrontal cortex and those amnesic patients with lesions to the basal forebrain/orbitofrontal cortex) did not show any evidence of implicit task sequence learning. In contrast, those amnesic patients with lesions to thalamic/medio-temporal regions showed intact sequence learning. Together, these results indicate that the integrity of the fronto–striatal system is a prerequisite for implicit task sequence learning.

1. Introduction

The ability to acquire and use knowledge involving structured sequences of events and actions is fundamental to adaptive behavior. Many skills, such as speaking and writing, using machinery and technical devices, driving, preparing meals, performing sport and music, comprise ordered regularities. Mostly, we do not give much thought to the precise order of our ideas and actions. They just seem to happen, either, because we have become competent through practice at an explicit goal-driven task and performance has become automatic, or else, we were never aware of any sequencing in the first place and learning has been incidental and unintentional (i.e., implicit). The serial reaction time task (SRTT; Nissen & Bullemer, 1987) provides an experimental analog of such implicit sequence learning. In this paradigm, a stimulus is presented at one of several horizontally distributed locations, and participants are required to respond to the location by pressing a corresponding key. Unbeknownst to them, the stimulus location (and thereby the motor response) is determined by a repeating sequence. With practice, response times decrease. However, when the sequence is replaced by a random order, response times then increase again substantially. This increase in response times is taken as indirect evidence of implicit sequence learning. Subsequent assessment of sequence awareness often reveals that knowledge of the sequence is implicit rather than explicit. Importantly, implicit learning of visuo-motor sequences has been found to be selectively impaired, or spared, in groups of patients with specific neurological disorders (e.g., Exner, Koschack, & Irle, 2002; Nissen & Bullemer, 1987; Siegert, Taylor, Weatherall, & Abernethy, 2006). It is only recently that a *task sequence learning* (TSL) paradigm has been introduced to examine cognitive rather than visuo-motor sequence learning. Here, we present the first study in which TSL in four different groups of patients exhibiting Parkinson's disease (PD), lesions in the ventromedial prefrontal cortex (VMPFC), lesions in the dorsolateral prefrontal cortex (DLPFC), or suffering from severe anterograde amnesia is tested.

Neuroimaging studies with healthy participants have demonstrated that a distributed network of cortical and subcortical areas is involved in ordinary implicit sequence learning using the SRTT (Curran, 1998). Although no clear consensus on the exact substrate of implicit sequence learning has been reached yet, the majority of

* Corresponding author at: Institute of Psychology, University of Bern, Fabrikstr. 8, 3012 Bern, Switzerland. Tel.: +41 31 631 40 39; fax: +41 31 631 82 12.
E-mail address: beat.meier@psy.unibe.ch (B. Meier).

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studies have found evidence for the involvement of the basal ganglia, motor cortical areas (primary motor cortex, premotor cortex, supplementary motor area), and the prefrontal cortex (e.g., Grafton, Hazeltine, & Ivry, 1995, 1998; Hazeltine, Grafton, & Ivry, 1997; Honda et al., 1998; Peigneux et al., 2000; Rauch et al., 1997). As the basal ganglia and the frontal cortex are highly interconnected by distinct parallel loops, recent models of implicit sequence learning have focused on the crucial role of the fronto–striatal circuitry in the acquisition and expression of sequence knowledge (e.g., Dominey & Jeannerod, 1997; Doyon et al., 2009; Doyon, Penhune, & Ungerleider, 2003; Nakahara, Doya, & Hikosaka, 2001).

At least five distinct fronto–striatal loops have been described that link specific regions of the frontal cortex to the basal ganglia: the motor circuit, the oculomotor circuit, the dorsolateral prefrontal circuit, the lateral orbitofrontal circuit, and the anterior cingulate circuit (Alexander, DeLong, & Strick, 1986). Each loop involves a separate part of the frontal lobe and includes discrete parts of the striatum (e.g., Alexander et al., 1986; Middleton & Strick, 2000, 2002; Postuma & Dagher, 2006).

Evidence from various clinical studies involving patients with neurological disorders also implicates an important role of the fronto–striatal circuitry for implicit sequence learning. Specifically, impaired implicit sequence learning has been found in patients with neurodegenerative diseases of the basal ganglia such as Huntington's disease (e.g., Kim et al., 2004; Knopman & Nissen, 1991; Willingham & Koroshetz, 1993; but see also Brown, Redondo-Verge, Chacon, Lucas, & Channon, 2001) and PD (Ferraro, Balota, & Connor, 1993; Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Muslimovic, Post, Speelman, & Schmand, 2007; Siegert et al., 2006; but see also Smith, Siegert, McDowall, & Abernethy, 2001; Smith & McDowall, 2006). Other studies have reported a deficit in implicit sequence learning in patients with frontal lobe lesions (Gómez Beldarrain, Grafman, Pascual-Leone, & Garcia-Monco, 1999; Gómez Beldarrain, Grafman, Ruiz de Velasco, Pascual-Leone, & Garcia-Monco, 2002), basal ganglia lesions (Vakil, Kahan, Huberman, & Osimani, 2000; but see Shin, Aparicio, & Ivry, 2005), and both basal ganglia lesions and additional frontal lobe lesions (Exner et al., 2002). In contrast, implicit sequence learning seems to be largely intact in amnesic patients with dysfunction or damage to the medial temporal or diencephalic circuitry (Nissen & Bullemer, 1987; Nissen, Willingham, & Hartman, 1989; Reber & Squire, 1994, 1998; but see Curran, 1997; Vandenberghe, Schmidt, Fery, & Cleeremans, 2006).

Whereas implicit sequence learning has been widely investigated across a variety of different clinical populations using the SRTT, this is the first study to examine implicit learning of *sequences of tasks* in different groups of patients. The task sequence learning (TSL) paradigm can be considered as an extension of the SRTT. In the TSL paradigm, participants respond to a series of different intermixed tasks. Unbeknownst to them, the order of the tasks is determined by a repeating sequence. However, within each task, the actual stimuli are presented at random. The stimuli belong to particular categories which are specific to a particular binary decision task (e.g., does a word belong to the category of mammals or birds? Does it belong to the category of trees or flowers? Does it belong to musical instruments or kitchen utensils?). As in the standard SRTT, response times decrease with practice and increase again substantially when the sequence is replaced by a random order of tasks or an untrained sequence. This increase is taken as indirect evidence of learning of the task sequence, or at least sensitivity to some aspects of it (Meier & Cock, 2010; Weiermann & Meier, 2012a). In the case of TSL, post-experimental assessment of awareness reveals that knowledge of the task sequence remains mostly implicit rather than explicit.

Our motivation for choosing the TSL paradigm over the SRTT was that we expected the TSL paradigm to be more sensitive for detecting cognitive changes than the standard SRTT because it requires higher-order cognitive processing. Specifically, in the TSL paradigm, each stimulus exemplar (e.g., the word "violin") has to be interpreted in terms of a higher-order concept (e.g., musical instrument vs. kitchen utensil) before the correct response can be made. These higher cognitive demands also pose additional requirements for the extraction of regularities which may be particularly dependent on the integrity of fronto–striatal circuitry. Furthermore, the sequence is *not* embedded in the order of stimuli, but rather in the superordinate order of tasks or stimulus categories and thus requires the formation of an abstract representation. Implicit task sequence learning has been established in a variety of different tasks, stimuli, modalities, sequences, and across the lifespan (Cock & Meier, 2007; Gotler, Meiran, & Tzelgov, 2003; Heuer, Schmidtke, & Kleinsorge, 2001; Koch, 2001; Meier & Cock, 2010; Meier, Weiermann, & Cock, 2012; Weiermann, Cock, & Meier, 2010; Weiermann & Meier, 2012a, 2012b).

In this study, participants were presented with three different categorical classification tasks (*animals*, *implements*, and *plants*). In each trial, a written stimulus word appeared centrally on the screen (see Fig. 1). When the word was an animal, participants were required to decide whether it was a bird or a mammal (*animals* task). When the word was an implement, they were required to decide whether it was a musical instrument or a kitchen utensil (*implements* task). When the word was a plant, they were required to decide whether it was a tree or a flower (*plants* task). Unbeknownst to participants, the order of the tasks was determined by a repeating sequence in most of the blocks. In a critical block, the sequence was replaced by an untrained sequence and sequence learning was assessed by comparing this block against the surrounding sequenced blocks. We expected that patients with affected fronto–striatal functioning would show a deficit in task sequence learning (Studies 1 to 3). We also expected that this deficit would be specific to these particular patient groups. Thus, we expected to find substantial task sequence learning in amnesic patients (Study 4).

2. General method

2.1. Participants

The patients were recruited from the Department of Neurology at the Bern University Hospital. All of them had German as their first language. Each study was approved by the local ethics committee and all participants agreed to take part by giving written informed consent.

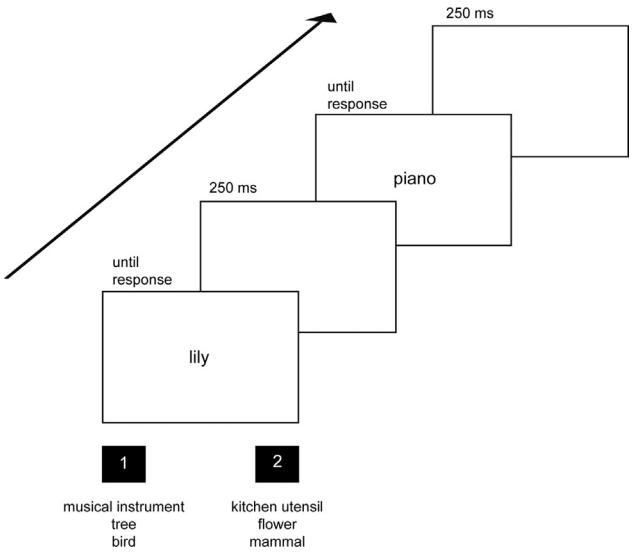

Fig. 1. Example of the task sequence learning paradigm.

2.2. Materials

Written words that can be classified into three different groups (i.e., implements, animals, or plants) were used as stimuli. The stimuli were selected such that implements were either *musical instruments* or *kitchen utensils*, animals were either *birds* or *mammals*, and plants were either *trees* or *flowers*. Each of these sub-groups (i.e., stimulus categories) had 16 exemplars each, such that 96 different words were used in total. Depending on tasks and trials, presentation of these exemplars varied at random with the only constraint being that each word occurred once per block. Stimuli were presented in German at the center of a 15-inch monitor in black 18-point courier new font against a white background. The study was run on an IBM-compatible laptop computer and was programmed in E-Prime (http://www.pstnet.com/e-prime).

Task order and response order were each sequenced according to one of two different 6-element repeating cycles. One task sequence was "plant–animal-implement-animal–plant-implement", accompanied by the repeating left (L) vs. right (R) key-press response order "L–R–L–L–R–R". The resulting stimulus category sequence (i.e., the sequence of category subdivisions) was "tree–mammal–musical instrument–bird–flower–kitchen utensil". The other task sequence was "implement-plant–animal–plant-implement-animal", accompanied by the response sequence "R–L–R–R–L–L". The resulting stimulus category sequence was "kitchen utensil–tree–mammal–flower–musical instrument–bird". Both sequences were used as training and transfer sequence, counterbalanced across participants.

2.3. Procedure

Participants were tested individually. They were told that the study concerned effects of practice on speed of performance of simple tasks. They were instructed to respond as quickly and as accurately as possible, and that if they made a mistake, they should simply continue. Instructions were given verbally and on screen.

Typically, participants responded with their right and left index fingers by pressing one of the two designated keys (L vs. R). However, in study 1, PD patients and healthy controls responded with their index and middle fingers of their dominant hand. This difference in response modality (one hand vs. two hands) was necessary due to asymmetric motor symptoms in PD patients. For the *implements* task, all participants pressed the L key for a *musical instrument* and the R key for a *kitchen utensil*. For the *plants* task, they pressed the (same) L key for a *tree* and the (same) R key for a *flower*. For the *animals* task, they pressed the (same) L key for a *bird* and the (same) R key for a *mammal*.

When the participant was ready, the experimenter pressed a key to initiate a block of trials. Each stimulus remained on screen until the participant pressed a response key. The next stimulus appeared after a delay of 250 ms. Each block consisted of 96 stimulus-response trials. Blocks were separated by short breaks. Two initial practice blocks (each comprising 16 repetitions of the transfer sequence) were used to train participants on the stimulus to response key mappings. The practice blocks were followed by four experimental blocks (blocks 3–6), each of which comprised 16 repetitions of the training sequence. In block 7, the transfer sequence was repeated 16 times. In block 8, the training sequence was reinstated and repeated 16 times.

After the test session, a structured interview was carried out to assess explicit knowledge of the sequences. Participants were first asked about the possible presence of sequenced information. Next, as appropriate, they were asked to verbally reproduce whatever they could still remember or guess of each of the sequences they had received (i.e., task sequence, stimulus category sequence, response sequence).

2.4. Data analysis

For response time (RT) analyses, trials on which errors were made, trials that followed an error, and the first six trials of each block were excluded. Median RTs per block and participant were computed for the three decision tasks separately. Then, the median RTs of the three tasks were averaged per block and participant. Decreasing RTs over blocks 3–6 were taken as directly indicative of a general training effect, also possibly including some sequence learning. *Training scores* were calculated, for each participant, as the RT difference between performance at block 3 and performance at block 6. Increased RTs at block 7 (where the training sequence was replaced by the transfer sequence) were taken as indirectly indicative of sequence learning. *Disruption scores* were calculated as the RT difference between performance at block 7 and mean performance at surrounding blocks 6 and 8. For all statistical analyses, an alpha level of.05 was used. For analysis of variance (ANOVA), Greenhouse-Geisser corrections are reported where appropriate and effect sizes are expressed as partial η^2 values. In order to quantify the sequence-specific learning, disruption scores were compared to zero and we used Cohen's d as measure of effect size (Cohen, 1977; Rosenthal, 1991), which allows an immediate evaluation of the size of the learning effect (i.e., $d=.20$ represents a small effect, $d=50$ represents a moderate effect and $d>.80$ represents a large effect).

3. Study 1: Parkinson's disease patients

In study 1, we investigated implicit task sequence learning in PD patients. Parkinson's disease is a neurodegenerative disease affecting the basal ganglia, and it is primarily characterized by motor symptoms such as resting tremor, bradykinesia, and rigor (see Lang & Lozano, 1998a, 1998b, for a review). However, PD patients also exhibit cognitive impairments including deficits in executive function. Disruption of fronto–striatal circuitry has been implicated in mediating these deficits (e.g., Taylor, Saint-Cyr, & Lang, 1986; Zgaljardic, Borod, Foldi, & Mattis, 2003; Zgaljardic et al., 2006).

Studies on implicit sequence learning in PD patients have revealed inconsistent results. Some authors have reported intact implicit sequence learning (e.g., Kelly, Jahanshahi, & Dirnberger, 2004; Smith et al., 2001), others have reported minor deficits in comparison to healthy controls (e.g., Ferraro et al., 1993; Muslimovic et al., 2007; Pascual-Leone et al., 1993; Shin & Ivry, 2003; Sommer, Grafman, Clark, & Hallett, 1999; Wilkinson & Jahanshahi, 2007; Wilkinson, Khan, & Jahanshahi, 2009), and yet others have reported a profound impairment (e.g., Jackson et al., 1995; Stefanova, Kostic, Ziropadja, Markovic, & Ocic, 2000). The discrepant findings between studies may be explained in part by differences in methods used in running the SRTT and by differences in sample characteristics. For example, the degree of implicit sequence learning seems to be related to the degree of clinical disability and medication (e.g., Doyon et al., 1997; Muslimovic et al., 2007; Price & Shin, 2009; Shanks, Wilkinson, & Channon, 2003; but see also Helmuth, Mayr, & Daum, 2000; Smith et al., 2001; Smith & McDowall, 2004; Stephan, Meier, Zaugg, & Kaelin-Lang, 2011), and to the level of cognitive functioning (Jackson et al., 1995; Price & Shin, 2009; but see also Muslimovic et al., 2007; Vandenbossche, Deroost, Soetens, & Kerckhofs, 2009). A recent meta-analysis concludes that implicit sequence learning is in fact impaired in PD patients (Siegert et al., 2006).

In line with these results, we expected to find impaired implicit task sequence learning in PD patients because PD may be considered as a particularly clear-cut example of dysfunction of the fronto–striatal circuitry (Zgaljardic et al., 2003).

Table 1
Clinical characteristics of the PD group ($n=14$)[1].

Variable	Range	*M*	SD
UPDRS motor section	6–41	26.0	12.3
AIMS passive	0–16	2.8	5.1
AIMS active	0–20	3.6	6.5
ADL (%)	70–100	89.6	6.3
LED (mg/day)	200–1471	718.5	348.7

Note: UPDRS motor section=Unified Parkinson's disease rating scale motor examination; AIMS=Abnormal involuntary movement scale; ADL=Schwab and England activities of daily living scale; LED=Levodopa equivalent dose.

[1] To examine whether the severity of motor symptoms affected sequence-specific learning in PD patients, a series of correlational analyses were carried out using Spearman's rho test. The *disruption score* was not significantly correlated with either UPDRS motor examination (rho=−.04, $p=.449$), or AIMS active (rho=−.02, $p=.474$), or AIMS passive (rho=−.06, $p=.422$), or Hoehn and Yahr stage of the disease (rho=−.07, $p=.403$), or Schwab and England ADL (rho=−.11, $p=.350$). This is in line with evidence from previous studies (Helmuth et al., 2000; Westwater, McDowall, Siegert, Mossman, & Abernethy, 1998; but see Muslimovic et al., 2007; Price & Shin, 2009). However, sample size was rather small and all PD patients were in their mild to moderate stages of disease (HYS 2–3). Thus, it is possible that a potential relationship between implicit sequence learning and progression of PD was not detected due to the homogeneity of the sample.

3.1. Method

3.1.1. Participants

Fourteen PD patients (11 male) with intact cognitive status, as indicated by performance the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) were included in the study ($M=29.3$; range 27–30). Mean age was 63.2 years ($SD=7.7$), and mean education was 12.7 years ($SD=1.61$). Verbal intelligence was assessed with the MWT-A, a German equivalent to the National Adult Reading Test (Lehrl, Merz, Burkhard, & Fischer, 1991). The mean verbal intelligence quotient (IQ) was 110.8 ($SD=15.8$). Patients were tested 3 to 18 years after the original diagnosis ($M=9.4$ years).

As a part of their ongoing neurological examination, clinical disability was assessed. The stage of disease was determined with the Hoehn and Yahr rating scale (Hoehn & Yahr, 1967). Nine patients were in stage 2, 1 patient in stage 2.5, and 4 patients in stage 3. Six patients had Levodopa (L-dopa) induced dyskinesias. Dyskinesias were assessed according to the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976) in both active and passive state. The duration of disease was defined as the time between the appearance of the first symptoms of PD, as reported by the patient, and the time of the study. Motor PD symptoms were rated using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn, Elton, & Members of the UPDRS Development Committee, 1987). Disability in performing everyday tasks was assessed according to the Schwab and England Activities of Daily Living (ADL) Scale (ADL; Schwab & England, 1969). The results are summarized in Table 1. The patients were also screened for depression (CES-D; Radloff, 1977), and did not differ from controls in their depression scores ($p>.05$).

All patients were treated with dopaminergic therapy and were following their routine medication regimen when tested. An L-dopa equivalence dose was calculated for each individual: 100 mg Madopar=100 mg Madopar liquid=75 mg Madopar DR/Sinemet CR=100 mg Sinemet CR & Comtan=130 mg Stalevo=10,000 mg Permax=1670 mg Requip/Adartrel=10,000 mg Sifrol=0 mg PKMerz. The L-dopa equivalence dose is also shown in Table 1. One participant was treated with deep brain stimulation of the subthalamic nucleus at the time of testing. The exclusion of this patient did not alter the results of the statistical analyses.

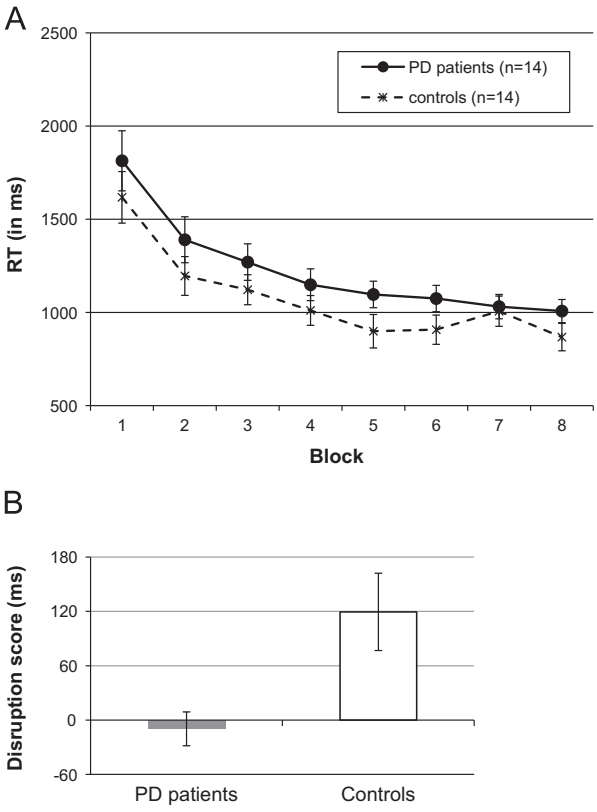

Fig. 2. (A) Reaction times of PD patients and matched healthy controls across blocks (Study 1). Block 3–6 and 8 are sequenced, block 7 is random. Implicit learning is expressed as slowing in random block 7 compared to the surrounding sequenced blocks. Error bars represent standard errors. (B) Sequence specific learning: disruption scores, calculated as performance in random block 7 compared to the mean of the sequenced surrounding blocks 6 and 8. Error bars represent standard errors.

After testing the patients, a control group was recruited which consisted of 14 healthy participants matched to the patients with regard to gender, handedness, age ($M=62.2$ years, $SD=8.0$), educational level ($M=13.6$ years, $SD=2.6$), and verbal intelligence (verbal IQ: $M=117.4$, $SD=18.2$). T-tests revealed no significant difference between groups (age, educational level, and verbal IQ, all $ps>.25$).

3.2. Results

3.2.1. Response accuracy

Mean accuracy rates (averaged from blocks 3–8) were.97 ($SE=.01$) for PD patients and .98 ($SE=.004$) for controls. The accuracy rates did not differ between groups, $t(26)=1.59$, $p=.124$.

3.2.2. Response times

The RT results are shown in Fig. 2A. RTs decreased initially for both groups, however, only controls appear to have been disrupted when the training sequence was replaced by the transfer sequence in block 7. Mean *training scores* (RT difference between blocks 3 and 6) were 196 ms ($SE=42$) for PD patients and 214 ms ($SE=32$) for controls. Mean *disruption scores* (RT difference between block 7 and mean of blocks 6 and 8), displayed in Fig. 2B, were −10 ms ($SE=19$) for PD patients and 120 ms ($SE=43$) for controls.

Statistical analyses were conducted separately for blocks 3–6 and blocks 6–8. A mixed 2×2 ANOVA with within-subjects factor block (block 3 vs. block 6) and between-subjects factor group (PD patients vs. controls) revealed a significant effect of block, $F(1, 26)=59.81$, $p<.01$, $\eta^2=.70$. Neither the effect of group nor the block × group interaction were significant, $Fs(1, 26)<2.0$, $ps>.15$, $\eta^2<.07$, indicating similar training effects in the two groups.

To assess sequence-specific learning, a separate 2×2 mixed ANOVA with within-subjects factor block (block 7 vs. mean RTs of block 6 and 8) and between-subjects factor group (PD patients vs. controls) was conducted. The effect of group was not significant, indicating similar RT levels in PD patients and healthy controls, $F(1, 26)=.80$, $p=.380$, $\eta^2=.03$. The effect of block was significant, $F(1, 26)=5.57$, $p=.026$, $\eta^2=.18$, and critically, the block × group interaction was also significant, $F(1, 26)=7.70$, $p=.010$, $\eta^2=.23$, indicating differences in sequence learning between the groups. To locate the source of the interaction, the *disruption scores* of the PD patients and of the controls were separately compared to zero in one-sample t-tests (cf. Fig. 2B). The *disruption score* of the PD patients was not significantly different from zero, $t(13)=-.52$, $p=.611$, $d=-.14$. This indicates that the PD patients did not learn the sequence. In contrast, the *disruption score* of the controls was significantly different from zero, $t(13)=2.80$, p(one-tailed)$=.008$, $d=.75$, indicating substantial sequence learning with a moderate to large effect size (Cohen, 1977; cf. Rosenthal, 1991).

When questioned afterwards, one PD patient was able to correctly report the whole response sequence. One control participant correctly reported the whole response sequence, the whole stimulus category sequence and the whole task sequence, another control participant correctly reported the whole response sequence and the whole stimulus category sequence, and two further controls correctly reported the response sequence. These five participants (1 patient, 4 controls) with potentially relevant explicit knowledge were excluded from the analysis. This resulted in mean *disruption scores* of −9 ms ($SE=20$) for PD patients and 67 ms ($SE=33$) for controls. The *disruption score* of the remaining controls was still significantly different from zero, $t(9)=2.06$, p(one-tailed)$=.03$, $d=.65$. Moreover, a direct comparison between the patients and the controls without explicit sequence knowledge also showed a significant difference, $t(20)=2.09$, $p<.05$, $d=.95$.

3.3. Discussion

As the performance of patients with PD was not disrupted when the training sequence was removed, we conclude that no significant implicit task sequence learning occurred. In contrast, the control group slowed down considerably, indicating that sequence learning took place. This difference in performance is not attributable to differences in explicit sequence knowledge: Even those healthy participants with no or little explicit knowledge were disrupted when the sequence was removed. This replicates our previous findings with healthy adults (e.g., Meier & Cock, 2010). Nevertheless, as this effect was tested one-sided, one may question the sensitivity of the TSL paradigm. However, we would argue that the one-sided test is theoretically justified. Besides, according to Cohen (1977), the size of the effect was still in the range of a moderate to strong effect. In contrast, the PD group did not show any learning at all and numerically the effect was even negative. Moreover, there was still a group difference in the disruption scores when the control group with no explicit knowledge was compared to the PD patients, thus suggesting that the sensitivity of the TSL to detect group differences is reasonable well.

The finding of impaired implicit sequence learning in PD patients is in line with findings from the SRTT literature. One possibility is that the lack of sequence learning might simply be due to frontal lobe dysfunction in the PD patients. However, there is convincing meta-analytic evidence for a striatal deficit in PD patients (e.g., Siegert, et al., 2006). Moreover, there is compelling evidence from neuroimaging studies that the striatal system is critically involved in implicit sequence learning which suggest that the integrity of the fronto–striatal circuits is critical for implicit sequence learning (e.g., Peigneux, et al., 2000). This makes it very unlikely that the lack of learning in the PD patients is simply due to frontal dysfunction. Rather, it is related to fronto–striatal dysfunction. Specifically, we suggest that the basal ganglia may have a crucial role, possibly through sequence integration (Shin, et al., 2005; Smith & McDowall, 2006). However, as PD is a neurodegenerative disorder affecting not only one circumscribed region of the brain, it is not possible to attribute the learning deficit to one specific part of the fronto–striatal circuitry.

Thus, in studies 2 and 3, we investigated implicit task sequence learning in patients with circumscribed lesions in regions of the frontal cortex which are part of different fronto–striatal loops, that is, regions within the ventromedial prefrontal cortex (VMPFC, study 2) and regions within the dorsolateral prefrontal cortex (DLPFC, study 3).

4. Study 2: patients with lesions in the ventromedial prefrontal cortex

In previous SRTT studies, implicit sequence learning was found to be impaired in patients with frontal lobe lesions (Gómez Beldarrain et al., 1999; Gómez Beldarrain et al., 2002), while explicit sequence learning was found to be intact (Koch, Reverberi, & Rumiati, 2006). Doyon et al. (1997) reported intact implicit sequence learning in patients with frontal lobe lesions. However, they only assessed a general training effect, which cannot be easily separated from sequence-specific learning. These studies included patients with lesions to various regions of the frontal cortex. In study 2, we report results from a sample of patients who had specific lesions to the VMPFC. In line with the hypothesis that VMPFC is critically involved in task sequence learning, we expected to find impaired implicit sequence learning.

4.1. Method

4.1.1. Participants

Twelve patients with VMPFC lesions (8 male) took part in study 2. Mean age was 44.6 years ($SD=14.8$), and mean education was 13.2 years ($SD=1.9$). Inclusion criteria were VMPFC lesions and the absence of severe amnesia. Nine patients had brain damage from traumatic brain injury, and two patients had brain damage following the bleeding from a ruptured aneurysm of the anterior communicating artery. One patient had brain damage following an olfactory meningioma. All of the patients had bilateral lesions. Fig. 3A shows the location and degree of overlap of brain lesions drawn on standard templates. Lesions were traced from the available CT or fMRI onto the standard Montreal Neurological Institute (MNI) brain using MRIcroN software (Rorden & Brett, 2000).

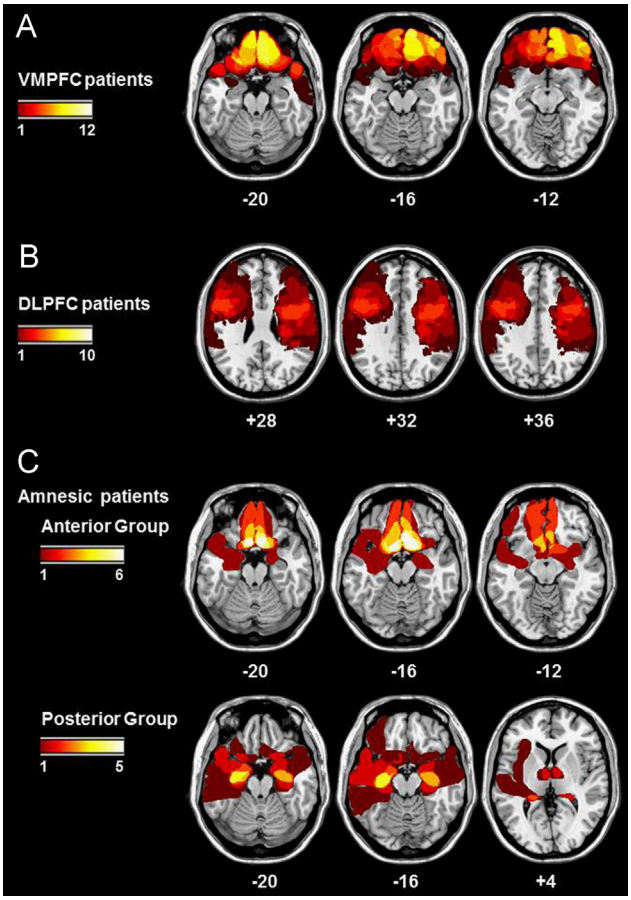

Fig. 3. Lesion location and overlap maps for (A) patients with VMPFC lesions, (B) patients with DLPFC lesions, and (C) for amnesic patients. Separate maps are shown for amnesic patients with lesions mainly to the basal forebrain ("anterior" group) and lesions mainly to the mesiotemporal lobe or the anterior thalamus ("posterior" group). Note, that the lesions of three patients in the posterior group with hypoxic brain damage were not drawn because no damage was visible on MRI. The color scale indicates the number of patients with damage to a particular area. The axis denotes *z*-values in Talairach space. For each group, the slices show the most affected levels of the brain. Left side is shown on the right side and vice versa.

Verbal Intelligence as assessed with the MWT-A (Lehrl et al., 1991) was 101.2 ($SD=13.9$). Memory was assessed with the VLMT (Helmstädter, Lendt, & Lux, 2001), a German equivalent to the Rey auditory verbal learning test (RAVLT). The mean age and education adjusted percentile score was 12.9 ($SD=10.7$) for word list learning and 8.8 ($SD=10.8$) for delayed free recall, indicating a slight episodic memory impairment. Patients were tested 7 months to 16.6 years after the incident leading to VMPFC lesion ($M=6.04$ years).

After testing the patients, a control group was recruited which consisted of 12 healthy participants matched to the patients with regard to gender, handedness, age ($M=44.2$ years, $SD=15.3$), and educational level ($M=13.44$ years, $SD=2.07$). *T*-tests revealed no significant differences between groups (all $ps > .5$).

4.2. Results

4.2.1. Response accuracy

Mean accuracy rates (averaged from blocks 3–8) were .95 ($SE=.01$) for patients and .98 ($SE=.01$) for controls, respectively. A *t*-test revealed a significant difference between groups, $t(22)=3.15$, $p < .01$. Due to the apparent ceiling effect, we do not discuss this result further.

4.2.2. Response times

The RT results are shown in Fig. 4A. RTs decreased initially for both groups, however, only controls appear to have been disrupted when the training sequence was replaced by the transfer sequence in block 7. Mean *training scores* (RT difference between blocks 3 and 6) were 219 ms ($SE=61$) for patients and 199 ms ($SE=37$) for controls. Mean *disruption scores* (RT difference between block 7 and mean of blocks 6 and 8), displayed in Fig. 4B, were −31 ms ($SE=23$) for VMPFC patients and 104 ms ($SE=29$) for controls.

Statistical analyses were conducted separately for blocks 3–6 and blocks 6–8. A mixed 2 × 2 ANOVA with within-subjects factor block (block 3 vs. block 6) and between-subjects factor group (VMPFC patients vs. controls) revealed a significant effect of block, $F(1, 22)=34.33$, $p<.01$, $\eta^2=.61$. There was also a significant effect of group, $F(1, 22)=10.73$, $p<.05$, $\eta^2=.33$, indicating the slower RTs of the VMPFC patients, but there was no block × group interaction, $F(1, 22)<1.0$, $p>.75$, $\eta^2=.004$, indicating similar training effects in the two groups.

To assess sequence-specific learning, a separate 2 × 2 mixed ANOVA with within-subjects factor block (block 7 vs. mean RTs of block 6 and 8) and between-subjects factor group (VMPFC patients vs. controls) was conducted. The effect of group was again significant, indicating slower RT levels in VMPFC patients than in the healthy controls, $F(1, 22)=10.92$, $p<.05$, $\eta^2=.33$. The effect of block was not significant, $F(1, 22)=3.9$, $p=.061$, $\eta^2=.15$. Critically, however, the block × group interaction was significant, $F(1, 22)=13.65$, $p=.001$, $\eta^2=.38$, indicating differences in sequence learning between the groups. To locate the source of the interaction, the *disruption scores* of the VMPFC patients and of the controls were separately compared to zero in one-sample *t*-tests (cf. Fig. 4B). Rather than being slowed, the VMPFC patients responded numerically even faster in block 7 compared to adjacent blocks, however, the difference was not significant, $t(11)=-1.37$, $p=.198$, $d=-.39$.

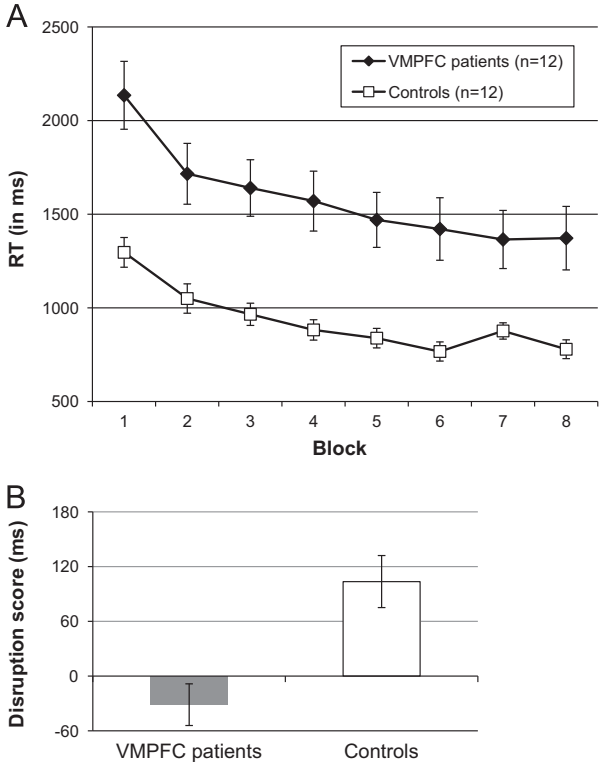

Fig. 4. (A) Reaction times of VMPFC patients and matched healthy controls across blocks (Study 2). Error bars represent standard errors. (B) Sequence specific learning: disruption scores. Error bars represent standard errors.

In contrast, the *disruption score* of the controls was significantly different from zero, $t(11)=3.63$, $p<.01$, $d=1.05$, indicating substantial sequence learning with a large effect size according to Cohen's interpretation.

These results provide no evidence for sequence learning in the VMPFC patients. When questioned afterwards, no patient was able to generate a sequence from memory, suggesting that relevant explicit sequence knowledge had not been acquired. Three control participants correctly reported the whole response sequence and the whole stimulus category sequence. These three participants with potentially relevant explicit knowledge were excluded from the analysis. This resulted in a mean *disruption scores* of 85 ms ($SE=31$) which was still significantly different from zero, $t(8)=2.45$, p (one-tailed) $<.05$, $d=.82$. Moreover, a direct comparison between the patients and the controls without explicit sequence knowledge also showed a significant difference, $t(19)=3.08$, $p<.01$, $d=1.42$.

4.3. Discussion

The patients with VMPFC lesions did not show any evidence of implicit task sequence learning. They did not slow down when the training sequence was removed. If anything, they tended to become even a little faster. The general, sequence-unspecific training effect and the high accuracy scores indicate that the patients were able to carry out the tasks. Thus, the lack of sequence learning cannot be attributed to task difficulty. The deficit in implicit sequence learning is in line with previous evidence and suggests that the VMPFC is certainly involved in implicit task sequence learning (Gómez Beldarrain et al., 1999, 2002).

In contrast, the control group showed a substantial learning effect, even after the exclusion of those participants with potential explicit knowledge. This result is consistent with study 1 and with our previous research, indicating the robustness and the reliability of task sequence learning in healthy controls. Nevertheless, we consider the lack of implicit task sequence learning of patients with VMPFC lesions the most important result of study 2.

5. Study 3: patients with lesions in the dorsolateral prefrontal cortex

5.1. Method

5.1.1. Participants

Nine patients (8 male) took part. Inclusion criteria were lesions in dorsolateral regions of the prefrontal cortex, absence of lesions to the basal ganglia and prefrontal areas other than the DLPFC, and absence of aphasia. Mean age was 49.9 years ($SD=13.2$), and mean education was 12.9 years ($SD=1.4$). Six patients suffered brain damage from cerebrovascular insult, one patient had brain damage following a tumor, one patient had brain damage following carotid artery dissection, and one patient had brain damage from traumatic brain injury (TBI). With the exception of the TBI patient, all patients had unilateral lesions. Fig. 3B shows the location and degree of overlap of brain lesions drawn on standard templates as in study 2.

Mean IQ as assessed with the MWT-A (Lehrl et al., 1991) was 93.1 ($SD=11.0$). For the VMLT, the mean age adjusted percentile score was 41.6 ($SD=28.1$) for word list learning and 40.7 ($SD=29.8$) for delayed free recall, indicating intact episodic memory. Patients were tested 2–5 years ($M=3.25$) after the incident leading to a DLPFC lesion.

After testing the patients, a control group was recruited which consisted of nine healthy participants matched to the patients with regard to gender, handedness, age ($M=53.5$ years, $SD=11.9$), and educational level ($M=14.3$ years, $SD=2.6$). *T*-tests revealed no significant age and education differences between groups (all $ps>.15$).

5.2. Results

5.2.1. Response accuracy

Mean accuracy rates (averaged from blocks 3–8) were close to ceiling, with .98 ($SE=.01$) for DLPFC patients and .99 ($SE=.006$) for controls and did not differ between groups, $t(16)=1.4$, $p=.179$.

5.2.2. Response times

The RT results are shown in Fig. 5A. RTs decreased initially for both groups, however, only controls appear to have been disrupted when the training sequence was replaced by the transfer sequence in block 7. Mean *training scores* (RT difference between blocks 3 and 6) were 116 ms ($SE=52$) for DLPFC patients and 129 ms ($SE=44$) for controls. Mean *disruption scores* (RT difference between block 7 and mean of blocks 6 and 8), displayed in Fig. 5B, were −4 ms ($SE=23$) for DLPFC patients and 111 ms ($SE=22$) for controls.

Statistical analyses were conducted separately for blocks 3–6 and blocks 6–8. A mixed 2 × 2 ANOVA with within-subjects factor block (block 3 vs. block 6) and between-subjects factor group (DLPFC patients vs. controls) revealed a significant effect of block, $F(1, 16)=13.13$, $p<.01$, $\eta^2=.45$. Neither the effect of group effect nor the block × group interaction were significant, $F(1, 16)=3.16$, $p=.09$, $\eta^2=.17$, and $F(1, 16)=.04$, $p>.80$, $\eta^2<.01$, respectively, indicating similar training effects in the two groups.

To assess sequence-specific learning, a separate 2 × 2 mixed ANOVA with within-subjects factor block (block 7 vs. mean RTs of block 6 and 8) and between-subjects factor group (DLPFC patients vs. controls) was conducted. The effect of group was not significant, indicating similar RT levels in DLPFC patients and healthy controls, $F(1, 16)=1.96$, $p=.18$, $\eta^2=.10$. The effect of block was significant, $F(1, 16)=11.01$, $p<.01$, $\eta^2=.41$, and critically, the block × group interaction was also significant, $F(1, 16)=12.68$, $p<.01$, $\eta^2=.44$, indicating differences in sequence learning between the groups. To locate the source of the interaction, the *disruption scores* of the DLPFC patients and of the controls were separately compared to zero in one-sample *t*-tests (cf. Fig. 5B). The *disruption score* of the DLPFC patients was not significantly different from zero, $t(8)=-.17$, $p=.87$, $d=-.05$. This indicates no evidence of sequence learning in DLPFC patients. In contrast, the *disruption score* of the controls was significantly different from zero, $t(8)=4.96$, $p<.01$, $d=1.65$, indicating substantial sequence learning with a strong effect sizes according to Cohen (1977).

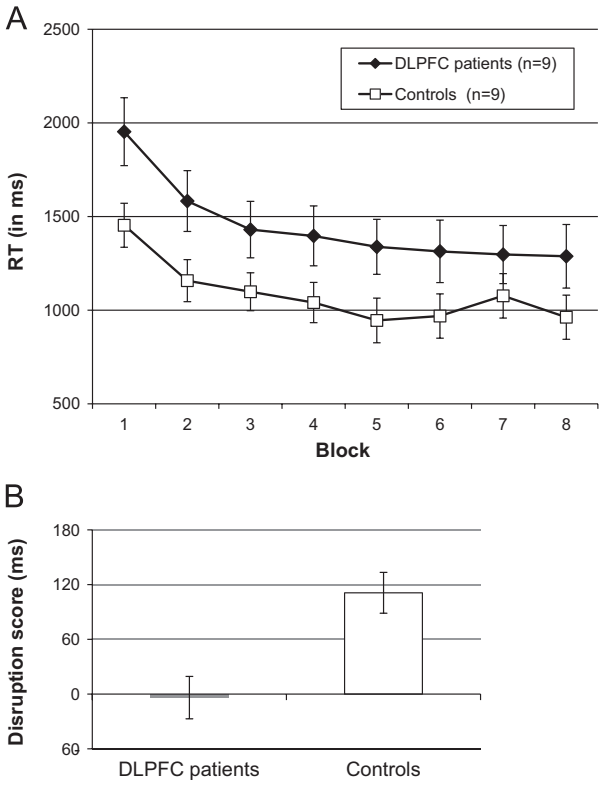

Fig. 5. (A) Reaction times of DLPFC patients and matched healthy controls across blocks (Study 3). Error bars represent standard errors. (B) Sequence specific learning: disruption scores. Error bars represent standard errors.

When questioned afterwards, none of the patients was able to correctly report any of the sequences suggesting that they did also not acquire any explicit sequence knowledge. Two control participants correctly reported the whole response sequence and one correctly reported the whole stimulus category sequence. When these three participants with potentially relevant explicit knowledge were excluded from the analysis, a mean *disruption score* of 103 ms ($SE=25$) resulted. This was still significantly different from zero, $t(5)=3.32$, $p<.05$, $d=1.36$. Moreover, a direct comparison between the patients and the controls without explicit sequence knowledge also showed a significant difference, $t(13)=3.07$, $p<.01$, $d=1.74$.

5.3. Discussion

Similar to VMPFC patients, DLPFC patients did not show evidence of implicit task sequence learning. Their performance was not disrupted when the task sequence was removed. Likewise, they did not acquire explicit sequence knowledge.

Assuming a crucial involvement of the fronto–striatal circuitry in implicit sequence learning, the observed impairment of both DLPFC and VMPFC patients is not surprising. In contrast to PD patients, the latter two groups of patients had circumscribed lesions within regions involved in fronto–striatal loops. Thus, the deficit in implicit sequence learning may be attributable directly to a disruption of these circuits.

In contrast, the control group showed substantial learning even when those participants with potentially relevant explicit knowledge were removed. This replicates the results from studies 1 and 2 as well as our previous findings, and corroborates the conclusion that the TSL paradigm is suitable to study learning deficits in patients with fronto–striatal disruptions. We consider the absence of implicit task sequence learning in patients with DLPFC lesions as the most important result of study 3.

However, rather than being specific to particular lesions, one might argue that general changes to the cognitive system may have affected performance of the patients. To test the specificity of the deficit, in study 4, we tested a group of densely amnesic patients. We considered that if this particular group showed implicit sequence learning, it would provide stronger evidence for the specificity of the lack of implicit task sequence learning in the groups with adversely affected fronto–striatal functioning.

6. Study 4: amnesic patients

In study 4, we tested amnesic patients. Only a few studies have investigated implicit sequence learning in amnesic patients (see Curran, 1998, for an overview). These studies suggest that amnesic patients can learn a repeating sequence without awareness (Curran, 1997; Nissen & Bullemer, 1987; Nissen et al., 1989; Reber & Squire, 1994, 1998; Vandenberghe et al., 2006). In line with these previous findings, we expected to find implicit task sequence learning effects in amnesic patients. We included a healthy control group to investigate whether this learning effect would be reduced in patients. We originally recruited as many amnesic patients as possible with a focus on an isolated, but severe and chronic episodic memory impairment. However, as amnesia does not only result from damage to the limbic system and the diencephalon, but also from damage to the basal forebrain and the posterior orbitofrontal cortex, that is, brain regions in the vicinity of the ventromedial prefrontal cortex, the underlying lesions were quite heterogeneous. For a follow-up analysis, we therefore separated the group of patients into those who had damage to the basal forebrain and orbitofrontal cortex ("anterior" group) and those who had more posterior damage ("posterior" group). In the "anterior" group we expected to find a sequence learning deficit due to disruption of the fronto–striatal circuitry. In contrast, in line with

previous SRTT studies, we expected to find intact implicit sequence learning effects in the "posterior" group.

6.1. Method

6.1.1. Participants

Fourteen amnesic patients (12 male) took part in this study. Inclusion criterion was the presence of severe, chronic episodic memory impairment. Mean age of the patients was 52.7 years (SD=9.9), and mean education was 14.9 years (SD=2.8).

Six patients had damage to the basal forebrain and orbitofrontal cortex ("anterior" group). Three had brain damage following bleeding from a ruptured aneurysm of the anterior communicating artery, two had suffered from herpes encephalitis, and one had damage following bleeding of a cavernoma. Eight other patients were considered to belong to the "posterior" group. Three showed amnesia following an episode of hypoxia. Although MRI did not reveal any visible brain damage, these patients were included in the "posterior" group since hypoxia is known to cause primarily damage to the hippocampus or adjacent regions (Zola-Morgan, Squire, & Amaral, 1986). Two had suffered bilateral thalamic infarction, one became amnesic following bleeding from an aneurysm of the middle cerebral artery, one due to damage to the hippocampus following lupus erythematosus, and one suffered from developmental amnesia with circumscribed lesions in the hippocampus due to birth complications. Fig. 3C shows the location and degree of overlap of brain lesions drawn on standard templates as in studies 2 and 3.

The mean verbal IQ was 112.4 (SD=15.0). For the VMLT, the mean percentile score was 1 (SD=2.3) for word list learning and .2 (SD=.8) for delayed free recall, documenting the severe episodic memory impairment. Patients were tested 5 months to 18 years after the incident leading to amnesia (M=9.3 years, SD=5.7), except for one patient who suffered from a developmental amnesia since birth.

After testing the patients, a control group was recruited which consisted of 14 healthy participants matched to the amnesic patients with regard to age (M=50.9 years, SD=12.8), educational level (M=15.1 years, SD=2.3) and IQ (M=114.8, SD=8.0). Independent t-tests revealed no significant difference between groups (age, educational level, and IQ, all $ps > .50$).

6.2. Results

6.2.1. Response accuracy

Mean accuracy rates (averaged from blocks 3–8) were .98 (SE=.01) for amnesic patients and .97 (SE=.005) for controls. Accuracy rates did not differ between groups, $t(26)$=.13, p=.901.

6.2.2. Response times

The RT results are shown in Fig. 6A separately for amnesic patients ("anterior" and "posterior" group combined) and controls. Response times decreased initially for both groups. Inspection of blocks 6–8 indicates that both amnesic patients and controls appear to have been disrupted by block 7 with the transfer sequence. Mean *training scores* were 207 ms (SE=57) for amnesic patients and 143 ms (SE=33) for controls. Mean *disruption scores*, depicted in Fig. 6B, were 48 ms (SE=25) for amnesic patients and 81 ms (SE=20) for controls.

Statistical analyses were conducted separately for blocks 3–6 and blocks 6–8. A mixed 2 × 2 ANOVA with within-subjects factor block (block 3 vs. block 6) and between-subjects factor group (amnesic patients vs. controls) revealed a significant effect of block, $F(1, 26)$=28.20, $p < .001$, η^2=.52, and a significant effect of group, $F(1, 26)$=16.77, $p < .001$, η^2=.39. The block × group interaction was not significant, $F(1, 26)$=.94, p=.342, η^2=.04. This indicates similar general training effects in both groups, even though amnesic patients responded more slowly than controls.

To assess sequence learning, a separate 2 × 2 mixed ANOVA with within-subjects factor block (block 7 vs. mean RTs of block 6 and 8) and between-subjects factor group (amnesic patients vs. controls) was conducted. Again, the significant effect of group indicated longer RTs in amnesic patients compared to controls, $F(1, 26)$=18.16, $p < .001$, η^2=.41. The effect of block was also significant, $F(1, 26)$=16.13, p=.003, η^2=.38. The block × group interaction was not significant, $F(1, 26)$=1.02, p=.322, η^2=.04, indicating similar sequence learning effects in both groups (cf. Fig. 6B), and a subsequent t-test revealed no significant group difference in *disruption scores*, $t(26)$=1.01, p=.320. Both the *disruption scores* of the amnesic patients and of the controls were significantly different from zero, $t(13)$=1.90, p(one-tailed)=.04, d=.51, and $t(13)$=4.08, p(one-tailed) < .001, d=1.09, respectively. This indicates implicit sequence learning in both groups.

In a follow-up analysis, the *disruption scores* of the patient groups were analyzed separately. For the "posterior" group, the *disruption score* was 73 ms (SE=23). This score was significantly different from zero, $t(7)$=3.13, p(one-tailed)=.009, d=1.11, indicating sequence learning. In contrast, the *disruption score* of the "anterior" group was 15 ms (SE=50). This score was not significantly different from zero, $t(5)$=.29, p(one-tailed)=.391, d=.12, indicating that in the subgroup of patients with anterior lesions learning was impaired. According to Cohen (1977) their disruption score would not even qualify as a small effect. For the sake of completeness, we also tested for differences between the disruption scores of the two subgroups. Due to the small sample size the t-test showed no significant difference, $t(12)$=1.15, p=.27, however the effect size was d=.67, which stills suggests that the difference between the groups was of moderate size.

When questioned afterwards, none of the patients was able to report any sequence correctly. This suggests that they did not acquire explicit sequence knowledge. Two controls correctly reproduced the whole response sequence (*disruption scores*=150 ms and 104 ms). In a follow-up analysis, these two participants were excluded. This resulted in a *disruption score* of 73 ms (SE=22) in the control group (n=12), which was still significantly different from zero, $t(11)$=3.28, p=.007, d=.95.

6.3. Discussion

Overall, the amnesic patients seemed to show intact implicit sequence learning. When taken together, their sequence-specific learning effect did not differ statistically from the learning effect of healthy controls. However, numerically, the learning score of the

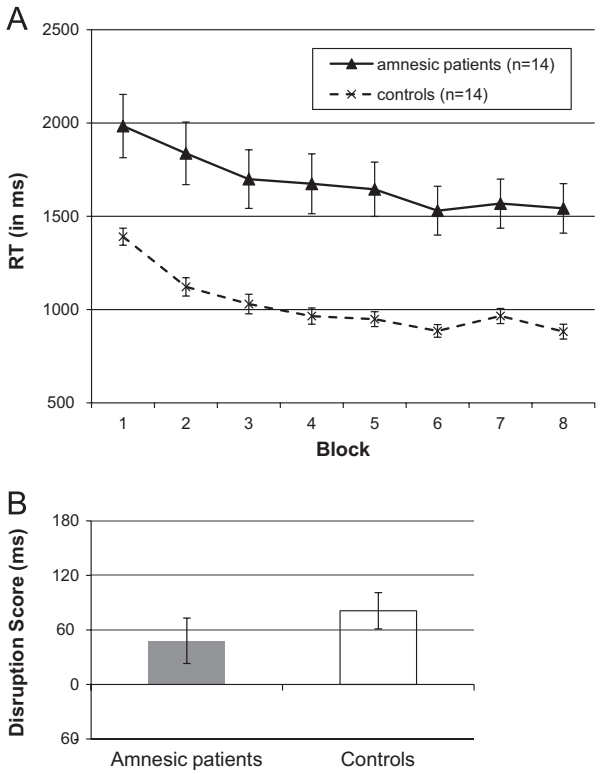

Fig. 6. (A) Reaction times of amnesic patients and matched healthy controls across blocks (Study 4). Error bars represent standard errors. (B) Sequence specific learning: disruption scores. Error bars represent standard errors.

amnesic patients was somewhat reduced. Importantly, this apparent reduction in sequence learning was attributable to the subgroup of patients who had lesions to the basal forebrain and the orbitofrontal cortex ("anterior" group), that is, to brain regions in the vicinity of the ventromedial prefrontal cortex. In fact, when analyzed separately, these particular patients did not show evidence of implicit sequence learning – possibly because their lesions affected the fronto–striatal circuit. This is in line with the lack of sequence learning effects found in patients with frontal lobe lesions (Studies 2 and 3). In contrast, those amnesic patients with more posterior lesions ("posterior" group) were able to learn the sequence in an implicit way, as indicated by their increase in response times when the sequence was removed. Although this latter result is suggestive and supports the specificity of the learning deficit for patient groups with affected fronto–striatal pathways, it is based on a rather small sample. Thus, a replication with a larger sample is required to provide more solid evidence.

7. General discussion

The goal of this project was to investigate the role of the fronto–striatal circuitry for implicit task sequence learning. We hypothesized that the integrity of the fronto–striatal loops is a precondition for the implicit learning of a sequence of simple decision tasks. To test this hypothesis we investigated performance of several patient groups whose etiology included compromised functioning of the fronto–striatal loops. In line with our expectations, patients with compromised fronto–striatal functioning such as those with Parkinson's disease, with lesions in the ventromedial prefrontal cortex, and with lesions in the dorsolateral prefrontal cortex did not show any sign of implicit task sequence learning. Similarly, amnesic patients with lesions in the basal forebrain showed a deficit in implicit sequence learning. In contrast, amnesic patients with lesions specific to more posterior areas (i.e., hippocampus and thalamus) showed intact task sequence learning.

This is the first study that tested patients across a range of fronto–striatal dysfunction by means of a task sequence learning paradigm. Although, in general, there has been considerable effort to explain what kind of mental or motor representation drives implicit sequence learning, there is still no consensus on what is involved. We suspect that this is related to the fact that typically, in most sequence learning studies there is a direct correspondence between the stimuli and the motor responses (i.e., isomorphic sequence structure). In several previous studies, we have used a task sequence learning paradigm in order to separate the stimulus sequence and the response sequence (Cock & Meier, 2007; Meier & Cock, 2010; Meier et al., 2012; Weiermann et al., 2010; Weiermann & Meier, 2012a). For example, we orthogonally combined a hidden task sequence with an independent hidden left vs. right response sequence. In those previous studies, learning effects were only found when the task sequence and the response sequence were of the same length, that is, when they were correlated. Only in this condition did the participants have the opportunity to integrate and use information from more than one source in order to anticipate subsequent tasks and responses. Thus, in the present study we have focused on this condition as it has produced robust and reliable sequence learning effects in healthy controls. Besides, in a number of follow-up studies, we have found that the presence of correlated input streams (i.e., streams of information) is important for implicit sequence learning to occur, irrespective of the particular type of information (Meier & Cock, 2010; Weiermann et al., 2010; Weiermann & Meier, 2012a). In fact, this is also the case in the SRTT where typically the sequenced order of the visuo-spatial positions of the stimulus is perfectly correlated with the sequenced order of the required responses. We have proposed elsewhere that the presence of correlated streams of information may thus be critically involved in many implicit sequence learning paradigms (cf., Meier & Cock, 2010; Meier et al., 2012; Weiermann et al., 2010).

Based on the results of the present study, we propose that this behavioral regularity may have its anatomical correspondence in the cooperation of different fronto–striatal loops. It has been suggested that each of the fronto–striatal loops is specialized for the processing of a certain kind of information (Alexander, Crutcher, & Delong, 1990; Alexander et al., 1986). Accordingly, the disruption of a particular circuit that is necessary for processing a specific stream of information would result in a loss of correlated information (i.e., loss of correspondence between different streams of information) and thus the lack of correlation could impede implicit sequence learning. For example, the motor circuit is specifically required for sequence learning that involves a motor response. This is necessary for most of the implicit sequence learning paradigms, including the task sequence learning paradigm used in the present study. Similarly, the oculomotor circuit is specifically involved in the processing of sequences that require stimulus processing at various different visuo-spatial locations. Hence, it is involved in the classical serial reaction time task, but not necessarily in the task sequence learning paradigm used in the present study. The prefrontal circuit is thought to be specifically involved in cognition that involves higher-order processing, including the shifting of task sets in implicit task sequence learning. The orbitofrontal circuit is thought to be particularly involved in decision making, as well as in emotional and motivational processing, and appears to be highly sensitive to the presence of reinforcement (Tekin & Cummings, 2002). Thus, it may also be generally involved in implicit sequence learning tasks.

Consequently, we would argue that a lack of integrity of one or more of these circuits, particularly in the patients with VMPFC lesions, DLPFC lesions, and lesions in the basal forebrain, as tested in the present study, is sufficient to explain the failure of implicit task sequence learning. Moreover, we propose that the frontal and the striatal systems fulfill different functional roles in the acquisition of implicit sequence learning. In particular, we suggest that the integrity of the striatal system is essential for extracting the parallel sequenced information, for synchronizing the input of the different streams of information, and for using the regularities of the correlations in order to fine-tune the cognitive system. In fact, we suggest that the integration of streams of correlated information is a pre-condition for implicit sequence learning. It seems very likely that PD patients, who have a deficit in the striatal system, are especially affected, in an adverse way, by the need to integrate any correlated streams of information. Similar notions have been put forward by others (Shin et al., 2005; Shin & Ivry, 2003; Smith & McDowall, 2006). From the assumption that distinct fronto–striatal circuits have separate functions, the hypothesis can be generated that, depending on the particular requirements of a sequence learning paradigm and the particular deficit of a patient group, dissociations between different groups of patients will occur. This is a promising avenue of investigation for disentangling the exact functions of different fronto–striatal loops.

So far, we have exclusively focused on the role of the fronto–striatal loops for implicit *task sequence learning*. From the general literature on implicit sequence learning, however, several other brain areas such as the cerebellum and the medial temporal lobe are often reported as interacting with the fronto–striatal system during implicit learning. Particularly, it has been suggested that the MTL is involved in the early acquisition phase (Albouy et al., 2008; Schendan, Searl, Melrose, & Stern, 2003) and for implicit learning of perceptual sequences (Rose, Haider, Salari, & Buchel, 2011). In contrast, the cerebellum is assumed to be involved in sensorimotor learning tasks (Hikosaka, Nakamura, Sakai, & Nakahara, 2002; Krakauer & Mazzoni, 2011; Penhune & Steele, 2012). However, as the focus of this project was on the role of the fronto–striatal system, we cannot assess the particular

contribution of the MTL and the cerebellum for implicit task sequence learning. To address this question future research is necessary.

The results of the present study clearly indicate that the integrity of the fronto–striatal system is a pre-condition for implicit task sequence learning. This is consistent with the results from the classical SRTT. The results are also consistent with the view that correlated streams of information may be necessary for this kind of implicit sequence learning and that these streams may be represented in separate cortico–striatal loops.

Acknowledgments

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