Timing Matters? Learning of Complex Spatiotemporal Sequences in Left-hemisphere Stroke Patients

Anna Dovern[1,2], Gereon R. Fink[1,2], David C. Timpert[1,2], Jochen Saliger[3], Hans Karbe[3], Peter H. Weiss[1,2], and Iring Koch[4]

Abstract

■ During rehabilitation after stroke motor sequence learning is of particular importance because considerable effort is devoted to (re)acquiring lost motor skills. Previous studies suggest that implicit motor sequence learning is preserved in stroke patients but were restricted to the spatial dimension, although the timing of single action components is as important as their spatial order. As the left parietal cortex is known to play a critical role in implicit timing and spatiotemporal integration, in this study we applied an adapted version of the SRT task designed to assess both spatial (different stimulus locations) and temporal (different response–stimulus intervals) aspects of motor learning to 24 right-handed patients with a single left-hemisphere (LH) stroke and 24 age-matched healthy controls. Implicit retrieval of sequence knowledge was tested both at Day 1 and after 24 hr (Day 2). Additionally, voxel-based lesion symptom mapping was used to investigate the neurobiological substrates of the behavioral effects. Although LH stroke patients showed a combined spatiotemporal learning effect that was comparable to that observed in controls, LH stroke patients did not show learning effects for the learning probes in which only one type of sequence information was maintained whereas the other one was randomized. Particularly on Day 2, patients showed significantly smaller learning scores for these two learning probes than controls. Voxel-based lesion symptom mapping analyses revealed for all learning probes that diminished learning scores on Day 2 were associated with lesions of the striatum. This might be attributed to its role in motor chunking and offline consolidation as group differences occurred on Day 2 only. The current results suggest that LH stroke patients rely on multimodal information (here: temporal and spatial information) when retrieving motor sequence knowledge and are very sensitive to any disruption of the learnt sequence information as they seem to build very rigid chunks preventing them from forming independent spatial and temporal sequence representations. ■

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021

INTRODUCTION

Throughout life, we acquire a multitude of motor skills. Many of these constitute complex action sequences comprising a number of elements. For example, everyday activities, like tying one's shoes or making tea, require the performance of single motor elements in the correct sequential order. Rehabilitation after stroke is a clinical setting in which motor sequence learning is of particular importance because a considerable amount of time is devoted to (re)acquiring motor skills.

As complex sequential activities are difficult to study in a laboratory setting, the SRT task was introduced to investigate motor sequence learning (Nissen & Bullemer, 1987). In the SRT task, participants respond to visual stimuli presented on a screen by pressing as fast and as accurately as possible the spatially congruent button on a keyboard. Unbeknown to the participants, stimuli are presented in a repetitive sequential manner in the majority of blocks. Shorter RTs in sequence blocks compared to RTs in blocks with randomly presented stimuli provide an indication of motor sequence learning. Given the incidental nature of the learning task, participants often show only little explicit sequence awareness, suggesting "implicit" learning (Schwarb & Schumacher, 2012).

The SRT task has been used to investigate motor sequence learning in stroke patients. With few exceptions (Boyd & Winstein, 2001), studies showed preserved implicit motor sequence learning in patients suffering from unilateral right-hemisphere or left-hemisphere (LH) stroke (Dovern et al., 2011; Boyd, Quaney, Pohl, & Winstein, 2007; Orrell, Eves, Masters, & MacMahon, 2007; Pohl & McDowd, 2006; Pohl, McDowd, Filion, Richards, & Stiers, 2001). Importantly, all these studies were restricted to examining learning in the spatial dimension (i.e., stimulus location) as they used either fixed response–stimulus intervals (RSIs) or no RSIs, hence neglecting stimulus timing, that is, temporal aspects of motor sequence learning. However, in real life, the correct timing of the elements of an action sequence is of equal importance.

A modified version of the SRT task allows assessing both spatial and temporal aspects of motor sequence

[1]University Hospital Cologne, [2]Research Centre Jülich, [3]Neurological Rehabilitation Centre Godeshöhe, Bonn, Germany, [4]RWTH Aachen University

© 2015 Massachusetts Institute of Technology

learning (Shin & Ivry, 2002). In this modified SRT task, the temporal sequence to be learned is realized by varying RSIs that follow a repetitive sequence as well. In the current study, we used spatial and temporal sequences of the same length (both nine-element sequences), which were always correlated throughout the learning phase. Importantly, this study design, introduced by Shin and Ivry (2002), allowed us to manipulate the temporal (stimulus timing) and spatial (stimulus location) sequences independently. That is, in addition to blocks containing the correlated spatial and temporal sequence pattern, it is also possible to create blocks that contain only one type of sequence information while the other one is randomized. As the variable RSIs result in more uncertainty about the appearance of successive stimuli, this version of the SRT task is more difficult in the first instance. However, once learned, the temporal sequence may contribute to better task performance, as participants may use both temporal and spatial information to predict the upcoming events (Coull & Nobre, 1998; Posner, 1980).

Neuroimaging studies on temporal orienting (or implicit timing) tasks consistently revealed activation of left parietal cortex, left premotor cortex (Coull, Davranche, Nazarian, & Vidal, 2013; Davranche, Nazarian, Vidal, & Coull, 2011; Coull & Nobre, 1998), as well as cerebellar activity (Coull et al., 2013; Coull & Nobre, 1998). Importantly, a meta-analysis on functional imaging studies investigating implicit timing tasks by Wiener, Turkeltaub, and Coslett (2010) revealed a single cluster of significant activation likelihood located in the left inferior parietal cortex (IPC). Because these tasks typically use speeded motor responses and because left parietal cortex has also been associated with motor intention and preparation (Hesse, Thiel, Stephan, & Fink, 2006; Thoenissen, Zilles, & Toni, 2002; Rushworth, Krams, & Passingham, 2001), it is important to note that temporal orienting activated left intraparietal sulcus even if the motor effector used for the response was unpredictable (manual vs. saccadic; Cotti, Rohenkohl, Stokes, Nobre, & Coull, 2011) and also in a purely perceptual rather than a speeded motor task (Davranche et al., 2011). Moreover, integrating spatial and temporal information has also been attributed to left parietal cortex (Assmus, Marshall, Noth, Zilles, & Fink, 2005; Assmus et al., 2003).

One important process underlying motor sequence learning is chunking (Sakai, Kitaguchi, & Hikosaka, 2003). Chunking means that the sequence to be learnt is divided into a number of subsequences (i.e., chunks) that are memorized as single units. Positions within a sequence at which there is a change in the pattern of movement (e.g., repetition, inversion) typically serve as chunk borders (Koch & Hoffmann, 2000). Likewise, a temporal delay in the RSI was shown to determine the chunking pattern (Stadler, 1993). However, even if the structure of the sequence itself does not imply a specific chunking pattern, a chunking pattern emerges, which may vary between participants performing the same sequence (Sakai et al., 2003). In the current study, the chunking process is emphasized as the variable RSIs may serve as natural chunking points. One key structure known to be critical for the chunking process is the striatum (Penhune & Steele, 2012; Orban et al., 2011; Graybiel, 1998).

In this study, we investigate whether patients with LH stroke are able to learn concurrently spatial and temporal aspects of motor sequences. It is assumed (Shin & Ivry, 2002) that three different types of learning, namely spatial, temporal, and relational learning, may contribute to RT advantages in blocks containing both the spatial and temporal sequences (compared to blocks that are randomized with respect to both the spatial and temporal dimensions). Therefore, learning effects in this learning probe are not necessarily indicative of both spatial and temporal sequence learning but could also result from learning either the spatial or the temporal sequence alone or from relational learning. To be able to differentially assess spatial and temporal learning, we included blocks comprising the learnt sequential information for one dimension (e.g., spatial), while they were randomized for the other dimension (e.g., temporal), and vice versa. These blocks thus provide information about whether participants learnt the spatial and/or the temporal sequence (as indicated by RT advantages compared to the block with completely randomized sequences). Additionally, we examined the retention of (spatial and temporal) motor sequence knowledge after 24 hr, because with respect to stroke rehabilitation, it is of great interest to assess whether patients are able to retrieve a learnt motor sequence after longer time intervals. We hypothesized that patients with LH stroke show preserved spatial but impaired temporal motor sequence learning.

Finally, voxel-based lesion symptom mapping (VLSM) was conducted to investigate the neurobiological substrates underlying the behavioral effects. Here, we conducted ROI analyses, focusing on the striatum because of its involvement in the chunking process underlying motor sequence learning and on the left IPC because of its role in temporal orienting and implicit timing. With respect to the striatum, we hypothesized that striatal lesions may either be associated with deficits in all three learning probes (i.e., spatial and temporal sequence information, only spatial sequence information, only temporal sequence information) as chunking is the underlying process for all of them or striatal lesions may be specifically associated with deficits of the learning probes containing only one type of sequence information as in these learning probes the initially formed chunks are disrupted and higher-order chunks (formed by only one type of information while ignoring the other type of information) need to be accessed. Moreover, we hypothesized that lesions of the parietal cortex are specifically associated with deficits of the learning probes containing temporal sequence information as the IPC is critically involved in processing temporal information.

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021

METHODS

Participants

Thirty-one patients suffering from a single (first ever) unilateral stroke affecting the left middle cerebral artery territory (two patients had a stroke additionally affecting the left anterior cerebral artery territory) and 24 healthy controls (mean age ± *SD*: 60.5 ± 12.7; 13 men) gave written informed consent before participating in the study. The study was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and approved by the local ethics committee of the Medical Faculty of the University of Cologne. All patients and controls were right-handed as assessed by the Edinburgh handedness inventory (Oldfield, 1971) and had normal or corrected-to-normal vision. Healthy control participants were screened for the history of any neurological or psychiatric disease by means of a structured interview. During the interview, the experimenter explicitly asked whether the participants previously experienced (symptoms of) a stroke or transient ischemic attack (TIA). All participants confirmed that they never experienced any symptom of a stroke or TIA. Patients were recruited prospectively during the subacute or chronic phase after stroke (i.e., >4 days poststroke). Patients had no psychiatric disorders including alcohol or drug abuse. Data of seven patients were excluded for the following reasons: initially unknown previous stroke (n = 1), presence of apraxia (n = 4; see below and Dovern et al., 2011) or massive prolongation of mean RTs (n = 2; deviating more than 2 *SD*s from the overall average RTs of all patients). Hence, statistical analyses were performed using data of 24 patients (mean age ± *SD*: 57.1 ± 10.41; 16 men; mean days poststroke ± *SD*: 117.5 ± 176.35; range = 23–780 days poststroke).

A number of clinical and neuropsychological tests were conducted in all patients to assess cognitive deficits commonly observed after LH stroke, that is, aphasia (the short version of the Aphasia Check List; Kalbe, Reinhold, Brand, Markowitsch, & Kessler, 2005) and apraxia (Cologne Apraxia Screening, Weiss, Kalbe, Kessler, & Fink, 2013; imitation of hand positions and finger configurations, Goldenberg, 1996; and actually using objects/tools, De Renzi, Pieczuro, & Vignolo, 1968). Following the procedures described in Dovern et al. (2011), a patient scoring below cutoff in at least one of the four apraxia tests was considered apraxic and therefore excluded (see above). To assess the degree of paresis, the Medical Research Council Scale (Medical Research Council of the United Kingdom, 1978) and the Action Research Arm Test (ARAT; Lyle, 1981) were applied to the affected (right) hand. The ARAT was applied to the left hand too and indicated that none of the patients suffered a functional impairment of the ipsilesional arm and hand as all patients achieved the maximum test score. Additionally, the modified Rankin Scale was used to assess general disability (Rankin, 1957). Moreover, the Corsi block tapping test, the Seashore Rhythm Test, and the Rey visual design learning test (recognition only) were applied in both patients and controls (Schellig, 1997; Spreen & Strauss, 1991; Seashore, Lewis, & Saetveit, 1960). Data are summarized in Table 1.

Stimuli and Material

Task and equipment of the original SRT paradigm (Nissen & Bullemer, 1987) were adopted for the purpose of (i) testing stroke patients (Dovern et al., 2011) and (ii) assessing temporal motor sequence learning (Shin & Ivry, 2002). Using Presentation software (Neurobehavioral Systems Inc., Berkeley, CA, Version 12.1), visual stimuli (black Xs) were presented successively at one of three possible horizontally aligned positions on a white screen. The three possible stimulus locations were highlighted continuously by gray squares indicating where stimuli could appear. All patients and controls were asked to respond as quickly and accurately as possible with their

Table 1. Patients' Characteristics

	Stroke Patients (n = 24)	*Healthy Controls (n = 24)*
Aphasia Check List (short version)	30.54 (±6.02)	
Medical Research Council Scale (right arm/right hand)	4.33 (±0.7)/3.98 (±1.26)	
Action Research Arm Test (right)	46.33 (±17.98)	
Action Research Arm Test (left)	57 (±0)	
Modified Rankin Scale	1.96 (±0.91)	
Corsi Block Tapping Test	4.71 (±0.91)	5.08 (±0.93)
Seashore Rhythm Test	23.95 (±3.09)	25.5 (±2.87)
Rey Visual Design Learning Test (Recognition Day 1/Recognition Day 2)	6.30 (±2.91)/4.13 (±2.8)	7.33 (±3.63)/5.58 (±2.86)

Means ± *SD*s are provided. None of the tests applied to both patients and controls differed significantly between groups at $p < .05$.

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021

nondominant (i.e., for patients the ipsilesional, nonparetic) left hand by pressing large buttons (spatially congruent with the stimulus presented) of a custom-made response board. The X remained visible until the participant responded. The subsequent X appeared after a variable RSI of 300, 600, or 1200 msec.

Procedure and Experimental Design

Within blocks, the position of the X either followed a nine-item spatial sequence (spatially structured sequence, SS-Sequence) or was presented pseudorandomly (spatially random sequence, SR-Sequence). Likewise, the RSI either followed a nine-item temporal sequence (temporally structured sequence, TS-Sequence) or was pseudorandomized (temporally random sequence, TR-Sequence). Four different types of blocks were constructed: (i) SS-TS blocks, (ii) SR-TS blocks, (iii) SS-TR blocks, and (iv) SR-TR blocks (Shin & Ivry, 2002). One block comprised five repetitions of the nine-item sequence, resulting in a block length of 45 trials.

In total, the experiment consisted of 12 blocks on the first day and of 6 blocks on the second day. On the first day, Blocks 1–4, 6–7, 9–10, and 12 were SS-TS blocks, whereas Blocks 5, 8, and 11 contained the other three types of blocks (SR-TS, SS-TR, SR-TR) in counterbalanced order across participants. The second day always started with a completely random block (SR-TR) to reacquaint participants with the task. Furthermore, on the second day, Blocks 2 and 6 were SS-TS blocks, whereas Blocks 3–5 contained the other three types of blocks (SR-TS, SS-TR, SR-TR) in counterbalanced order across participants. For an overview of the block order on the 2 days, please see Table 2. Between blocks, breaks were implemented, so that participants could decide in a self-paced manner when to continue with the next block.

In the current experiment, nine-item sequences of similar statistical structure were used both for the spatial and temporal sequence. The sequences contained ambiguous serial transitions (Cohen, Ivry, & Keele, 1990), meaning that each stimulus was followed by different stimuli at different points in the sequence. More specifically, each stimulus location occurred three times and was in each case followed by a different stimulus location (e.g., Stimulus 1 occurs three times within the sequence and is followed once by every stimulus location—also allowing repetitions of stimulus locations). Thus, to implicitly anticipate the next response, implicit knowledge about the two preceding items was required. The sequences were constrained by the fact that sequences were not allowed to contain a complete run with stimuli appearing successively from left to right or vice versa (i.e., 1-2-3 or 3-2-1). Another restriction was that not all three stimulus repetitions comprised in the sequence followed each other. Given these constraints, four 9-item sequences were selected to be used in the current study. The four sequences were used to create two different versions of the experimental paradigm to ensure that any effects found are not specific for a given sequence but generalizable to different sequences. The following sequences were used in version one: 1-1-2-1-3-3-2-2-3 (spatial sequence) and 1-1-3-2-3-3-1-2-2 (temporal). In the second version, the following sequences were used: 1-1-2-2-1-3-3-2-3 (spatial sequence) and 1-1-3-2-2-3-3-1-2 (temporal sequence). For the spatial sequences, 1 represents the left, 2 the middle, and 3 the right stimulus location. For the temporal sequences, 1 represents an RSI of 300 msec, 2 an RSI of 600 msec, and 3 an RSI of 1200 msec. In SS-TS blocks, the spatial and temporal sequences were always correlated with the same phase relationship across blocks,

Table 2. Arrangement of Blocks on Day 1 and Day 2

Block Number	*Locations*	*RSIs*
Day 1		
Learning—Day 1		
1	sequenced	sequenced
2	sequenced	sequenced
3	sequenced	sequenced
Retrieval—Day 1		
4	sequenced	sequenced
5	**random**	**sequenced**
6	sequenced	sequenced
7	sequenced	sequenced
8	**sequenced**	**random**
9	sequenced	sequenced
10	sequenced	sequenced
11	**random**	**random**
12	sequenced	sequenced
Day 2		
Retrieval—Day 2		
1	random	random
2	sequenced	sequenced
3	**random**	**sequenced**
4	**sequenced**	**random**
5	**random**	**random**
6	sequenced	sequenced

Day 1 comprised a learning phase (Blocks 1–3) and a retrieval phase (Blocks 4–12), whereas Day 2 comprised a retrieval phase only.

Please note that on Day 1 Blocks 5, 8, and 11 (printed in **bold**) were presented in counterbalanced order across participants. Likewise, on Day 2 Blocks 3, 4, and 5 (printed in **bold**) were presented in counterbalanced order across participants.

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021

as it was shown in healthy participants that a separate representation of the temporal sequence was formed only when spatial and temporal sequences were correlated during the learning phase (Shin & Ivry, 2002). Importantly, the pseudorandom sequence was designed to have, across the whole block, the same item frequency of all three stimulus locations as well as the same first-order transition probabilities as the sequenced blocks. Hence, differences between the structured and pseudorandom blocks only refer to differences in serial transitions that go beyond the level of stimulus pairs (Hoffmann & Koch, 1998; Reed & Johnson, 1994).

Note that before the experiment, participants were not informed about the sequential order of stimulus presentation. After completion of the task (i.e., on Day 2), the amount of (incidentally) learnt spatial and temporal sequence knowledge that participants were able to retrieve intentionally was assessed by a standardized, structured interview and a free recall test (for a detailed description, see Dovern et al., 2011). Explicit knowledge of the spatial sequence was parameterized as the longest continuous series of button presses that matched the actual sequence (Koch, 2007). An analogous interview and free recall task were also conducted for the temporal sequence.

Data Analysis

We performed statistical analyses using the statistical software package SPSS (IBM, version 21, Armonk, NY). Error trials were defined as trials in which participants responded by pressing an incorrect (spatially noncongruent) button. Before RTs were analyzed, error trials were discarded. Then the median RT per block was calculated for each individual participant. As the SS-TS condition was repeatedly presented during the retrieval phases on Day 1 (Blocks 4, 6–7, 9–10, and 12) and Day 2 (Blocks 2 and 6; see also above and Table 2), the mean of the median RTs of these blocks was calculated separately for Day 1 and Day 2. Learning scores were computed separately for Day 1 and Day 2 by subtracting the median RT of the SS-TR block and of the SR-TS block from the median RT of the SR-TR block. Learning scores for the SS-TS condition (containing multiple SS-TS blocks) were calculated separately for Day 1 and Day 2 by subtracting the mean of the median RTs of the SS-TS blocks (see above) from the median RT of the SR-TR block.

Lesion Mapping and Analyses

Figure 1A depicts the lesion pattern of the 22 patients of whom a CT or MRI scan was available for lesion mapping. For lesion analysis, the free MRIcron software (www.mccauslandcenter.sc.edu/mricro/mricron/index.html) was employed. All lesions were mapped by drawing the lesions manually on a T1-weighted template brain (ch2.nii) provided by MRIcron. Lesions were drawn onto axial slices that corresponded to the *z*-coordinates from −42 to +78 in steps of 5 mm (Montreal Neurological Institute [MNI] space). Lesion mapping was performed by AD and

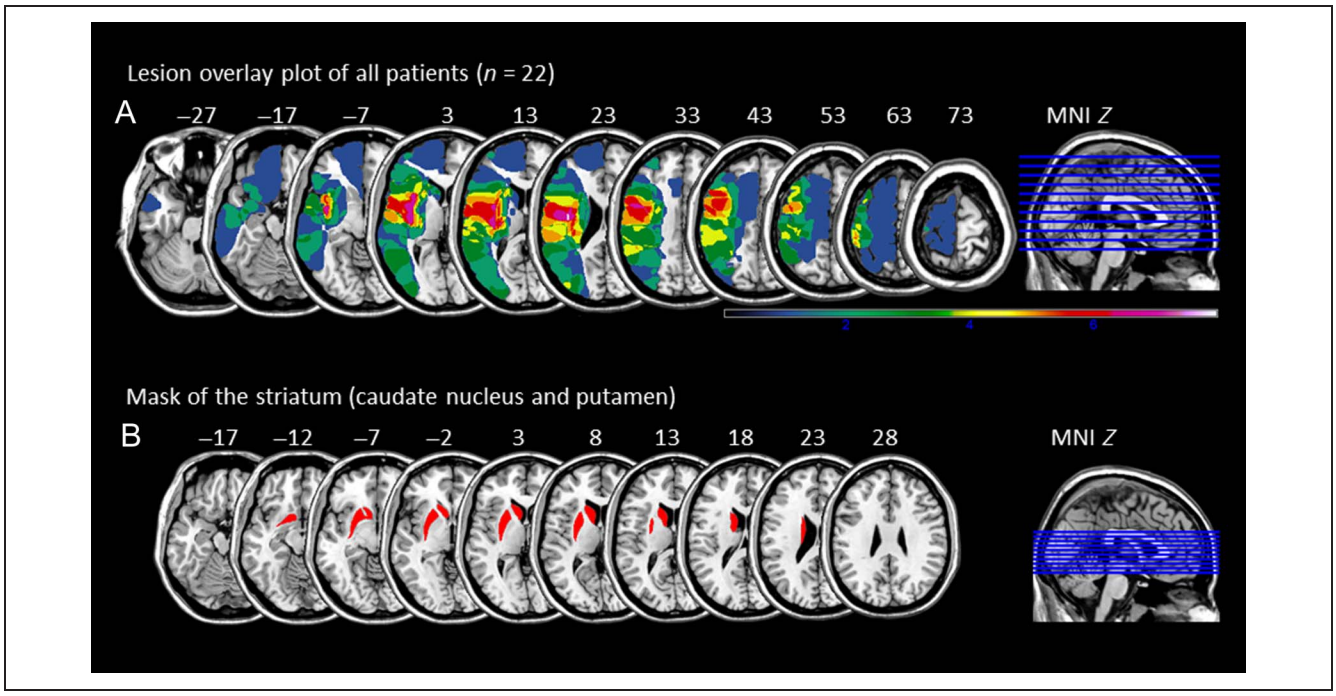

Figure 1. (A) Lesion overlay of patients suffering from LH stroke (n = 22). The color bar indicates the number of patients with a lesion in the region that is colored, respectively. Axial slices from MNI *Z*-coordinates −27 to 73 are shown. (B) Mask of the striatum (caudate nucleus and putamen) used for ROI analyses. Axial slices from MNI *Z*-coordinates −17 to 28 are shown.

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021

checked by DCT. Both investigators had to jointly agree upon lesion location and extent in each patient and had no knowledge of the patient's test performance and ratings at the time of mapping. MRIcron was used to perform statistical VLSM, which avoids grouping patients according to lesion site or behavioral cutoff scores but rather uses continuous behavioral and lesion information (Rorden, Karnath, & Bonilha, 2007; Bates et al., 2003). That is, in VLSM analyses, patients are divided into two groups on a voxel-wise basis depending on whether a given voxel in the brain is affected by a patient's lesion or not. Behavioral parameters can then be statistically compared between these groups of patients (with or without damage in that voxel) for each voxel by means of two-sample t tests. Only voxels that were damaged in at least 10% of the patients were tested. Voxel-wise t tests were performed and are reported at $p < .05$ (FDR-corrected) with a cluster threshold of 5 voxels.

In addition to the whole-brain analysis, ROI analyses were performed. ROI analyses of the left IPC were conducted as spatiotemporal integration and implicit timing (the specific aspects of interest of the current SRT task version) have been shown to specifically rely on that region (Wiener et al., 2010; Assmus et al., 2005). The coordinates reported in these studies (−60/−42/30 for spatiotemporal integration and −56/−42/30 for implicit timing) lie well within IPC. For the ROI analyses, a mask of the IPC was created using the anatomy toolbox (Eickhoff et al., 2005). Additionally, ROI analyses for the striatum (i.e., caudate nucleus and putamen; see Figure 1B for the mask used for the ROI analysis) were conducted: Previous neuroimaging studies revealed that implicit motor sequence learning relies on a subcortical–cortical network in which the striatum constitutes a key node (Rieckmann, Fischer, & Bäckman, 2010; Reiss et al., 2005; Daselaar, Rombouts, Veltman, Raaijmakers, & Jonker, 2003; Peigneux et al., 2000; Hazeltine, Grafton, & Ivry, 1997). Moreover, the striatum plays a critical role in chunking, which is a key process underlying motor sequence learning (Penhune & Steele, 2012; Orban et al., 2011; Graybiel, 1998).

RESULTS

Behavioral Data: Error Rates

Neither for Day 1 nor for Day 2 did overall error rates differed significantly between LH stroke patients and healthy controls (Day 1: $t(46) = 0.933$, $p = .356$; Day 2: $t(46) = 1.304$, $p = .199$). Mean error rates were smaller than 1% in both groups on both days (mean ± SD): 0.33 ± 0.55% (Day 1) and 0.38 ± 0.58% (Day 2) for stroke patients and 0.20 ± 0.35% (Day 1) and 0.18 ± 0.48% (Day 2) for healthy controls. Because of this floor effect, error rates provided no suitable measure for the learning effect and hence were not further analyzed. For that reason, statistical analyses were restricted to the RT data.

Behavioral Data: RTs

General Learning Effect

To examine general practice benefits for the combined spatial-temporal sequence, we analyzed the performance during the learning phase (Block 1–Block 3) by conducting a 2 (Group: LH stroke vs. controls) × 2 (Block: Block 1 vs. Block 3) mixed-design ANOVA. This analysis showed a significant main effect of Block ($F(1, 46) = 67.404$, $p < .001$), indicating that RTs decreased from Block 1 to Block 3. The main effect of Group ($F(1, 46) = 1.713$, $p = .197$) and the interaction between Block and Group ($F < 1$) were not significant. These results indicate that there was no significant difference in general response speed between LH stroke patients and controls and that the general practice benefit was of equal size in both groups.

Sequence-specific Learning Effects

To analyze RTs of the retrieval phases at Day 1 and Day 2 (i.e., the sequence-specific learning effect), the manipulations of spatial and temporal sequence structure were treated as two independent variables. Accordingly, we ran a 2 (Spatial structure: sequenced vs. random) × 2 (Temporal structure: sequenced vs. random) × 2 (Day: Day 1 vs. Day 2) × 2 (Group: LH stroke vs. controls) mixed-design ANOVA (see Figure 2A). Conducting this ANOVA, we obtained significant main effects for Spatial structure ($F(1, 46) = 51.037$, $p < .001$), Temporal structure ($F(1, 46) = 11.771$, $p = .001$), and Day ($F(1, 46) = 42.723$, $p < .001$). The main effect of Day indicated that participants responded generally faster on Day 2 than on Day 1. Moreover, the main effects for Spatial structure and Temporal structure indicated that participants responded faster when stimuli were presented according to the learned spatial and temporal sequential pattern as when stimuli were presented at randomized locations or with randomized RSIs.

Moreover, the ANOVA revealed a significant two-way interaction of Spatial structure and Temporal structure ($F(1, 46) = 9.626$, $p = .003$), indicating that the effect of spatial structure was greater when the temporal structure was present relative to when it was absent. The main effect of Group and all other two- and three-way interactions were not significant (all ps > .1).

Importantly, the four-way interaction was significant (Spatial structure × Temporal structure × Day × Group; $F(1, 46) = 4.527$, $p = .039$). To understand how differences between healthy controls and LH stroke patients led to the significant four-way interaction, we conducted two 3-way ANOVAs for the two days separately. Again both analyses revealed significant main effects for the factors Spatial structure and Temporal structure (Spatial structure: $F(1, 46) = 26.228$, $p < .001$, Temporal structure: $F(1, 46) = 4.448$, $p = .04$ for Day 1; Spatial structure: $F(1, 46) = 40.760$, $p < .001$, Temporal structure: $F(1, 46) = 7.718$, $p = .008$ for Day 2). The interaction between Spatial

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021

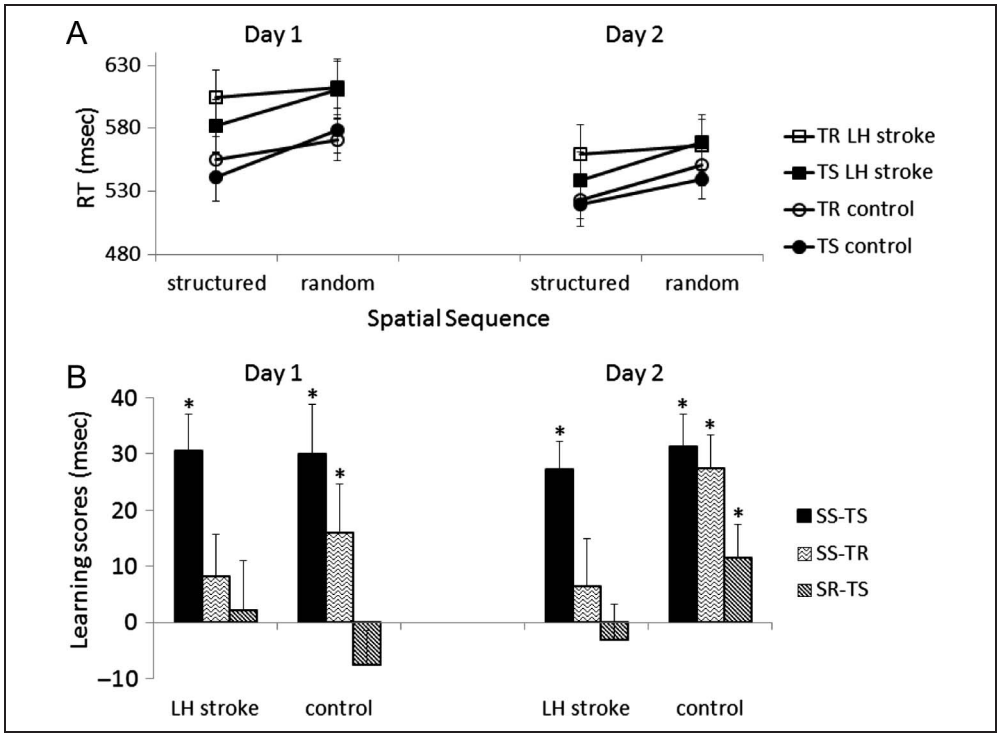

Figure 2. (A) RT patterns of patients suffering from LH stroke (squares) and healthy controls (circles) in the four different conditions (i.e., SS-TS, SS-TR, SR-TS, SR-TR) during the retrieval phases on Day 1 and Day 2. (B) Learning scores (i.e., RT advantages compared to the SR-TR condition) for the conditions containing either spatial (SS-TR) or temporal (SR-TS) information in isolation or both types of sequence information in combination (SS-TS). Learning scores are depicted for stroke patients and controls for Day 1 and Day 2, separately. LH stroke = patients suffering from left-hemisphere stroke; control = control participants; SS = spatially structured; SR = spatially random; TS = temporally structured; TR = temporally random; *$p < .05$ (one-tailed one-sample t tests).

structure and Temporal structure was significant on Day 1 ($F(1, 46) = 11.775, p = .001$) but not on Day 2 ($F(1, 46) = 1.793, p = .187$), indicating that only on Day 1 was the effect of spatial structure greater when the temporal structure was present relative to when it was absent. Neither for Day 1 nor for Day 2 were any of the other two-way interactions significant (all $p \geq .222$). Interestingly, although there was no significant three-way interaction (Spatial structure × Temporal structure × Group) on Day 1 ($F < 1$), the three-way interaction was significant on Day 2 ($F(1, 46) = 6.867, p = .012$), indicating that significant group differences emerged on Day 2 only.

Learning scores (defined as RT advantages compared to the SR-TR block) of patients and controls were used to quantify the benefits derived from spatial and temporal sequence information (presented in combination or isolated) on Day 1 and Day 2 to further elucidate this finding (see Figure 2B). One-sample t tests (one-sided, as we predicted that participants benefited from the spatial and/or temporal sequence information) revealed the following pattern (see Figure 2B): Stroke patients showed significant RT advantages on both days only when spatial and temporal sequence information was provided in combination (SS-TS: Day 1: $t(23) = 4.72, p < .001$ and Day 2: $t(23) = 5.302, p < .001$; all other learning scores were nonsignificant with $p \geq .14$). Control participants also showed significant RT advantages for combined spatial and temporal sequence information (SS-TS: Day 1: $t(23) = 3.356, p < .01$ and Day 2: $t(23) = 5.416, p < .001$; see Figure 2B). Control participants additionally benefitted from isolated spatial sequence information (on Day 1: $t(23) = 1.849, p = .039$ and Day 2: $t(23) = 4.703, p < .001$) and from isolated temporal sequence information (on Day 2 only: $t(23) = 1.932, p = .033$). To further elucidate differences between groups, we subjected learning scores to independent two-sample t tests. These confirmed that groups did not differ significantly on Day 1 but that differences between groups emerged on Day 2 for the learning probes, maintaining only one type of sequence information while randomizing the other one (i.e., SS-TR and SR-TS; for details, see Table 3).

Free Recall Data

Although most LH stroke patients and controls had recognized that intervals between a response and the next stimulus were of different durations, nearly all of them refused to have a guess about the precise temporal sequence. Therefore, these data were not further analyzed, and statistical analysis was confined to the explicit retrieval of the spatial sequence. The discrepancy between explicit retrieval of sequence knowledge for the temporal and spatial sequence is in agreement with previous findings (Shin & Ivry, 2002). The most parsimonious explanation for this discrepancy is that the responses are directly dependent on the stimulus location (spatial structure; pressing a spatially congruent button) rather than the RSI (temporal structure).

LH stroke patients explicitly retrieved significantly less spatial sequence knowledge than healthy controls (LH stroke: 3.04 ± 1.43 sequence elements, controls: 3.83 ± 1.2 sequence elements, $t(46) = 2.076, p = .044$). This difference could not be attributed to a limited visuospatial working memory capacity, because the two groups did

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021

Table 3. Learning Scores for Day 1 and Day 2

	Day 1					*Day 2*				
	LH Stroke	*Control*	*Δ*	*t*	*p*	*LH Stroke*	*Control*	*Δ*	*t*	*p*
SS-TS	31	30	−1	−0.07	.474	27	31	4	0.55	.294
SS-TR	8	16	8	0.68	.250	7	28	21	2.07	.022**
SR-TS	2	−8	−10	−0.93	.179	−3	12	15	1.67	.051*

Learning scores are defined as RT advantages in the different learning probes (i.e., SS-TS, SS-TR, SR-TS) compared with RTs in the block containing both a randomized spatial and a randomized temporal sequence structure.

The mean learning scores for stroke patients and controls are provided (in msec). Moreover, the mean RT difference (Δ) between controls and patients for each learning probe is provided as well as the t and p values belonging to the respective independent two-sample t tests (one-tailed).

*$p < .10$.

**$p < .05$.

not differ significantly with respect to the Block Tapping Test (LH stroke: 4.71 ± 0.908, controls: 5.08 ± 0.929 (controls), $t(46) = 1.415$, $p = .164$). Moreover, neither in patients nor in controls was explicit sequence knowledge (maximum number of correctly retrieved sequence elements) significantly correlated with the Block Tapping Test score ($r = 0.01$, $p = .964$ [LH stroke]; $r = -0.259$, $p = .221$ [controls]). As sequence awareness was assessed on Day 2 only, correlations between explicit sequence knowledge and the three different learning scores on Day 2 were examined to uncover a possible influence of sequence awareness on sequence learning. However, neither for patients nor for controls did the correlation analyses reveal a significant association between explicit sequence knowledge and any of the learning scores (all ps ≥ .17, see Table 4). Furthermore, we examined the influence of sequence awareness on general performance by looking at the correlation between explicit sequence knowledge and the mean RT of the SS-TS blocks (Blocks 1–4) before the first transfer block. Again, neither group showed a significant association between the two measures ($r = 0.127$, $p = .553$ for patients and $r = -0.018$, $p = .935$ for controls). Given that in both groups knowledge about the spatial sequence remained rather implicit (i.e., retrieval of fewer than four of nine sequence elements) and that the degree of explicit sequence knowledge had no impact on sequence learning and general performance, the free recall data are not discussed further.

Table 4. Correlation Coefficients for the Correlation of Explicit Sequence Knowledge Scores and the Three Learning Scores on Day 2 for Patients with LH Stroke and Healthy Controls

Group	*SS-TS*	*SS-TR*	*SR-TS*
LH stroke	−0.14	−0.27	−0.29
control	0.04	−0.24	−0.06

Note, all with $p \geq .17$.

Lesion Data

Group differences between LH stroke patients and healthy controls emerged on Day 2 only. Therefore, the VLSM analyses focused on identifying the lesion sites associated with diminished learning effects on Day 2. To this end, separate VLSM analyses were conducted with the three learning scores (SS-TS, SS-TR, SR-TS) of Day 2 as dependent variables.

Although the whole-brain analyses and the ROI analyses covering the left IPC did not reveal any significant lesion–symptom association, the ROI analyses comprising the left striatum revealed significant associations for all three learning scores. More specifically, a diminished ability to learn the integrated spatiotemporal motor sequence (SS-TS probe) was associated with lesions affecting the putamen and caudate nucleus (see Figure 3A), whereas deficits on the learning probes where only one type of information was provided (i.e., SS-TR probe and SR-TS probe) were specifically associated with lesions of the caudate nucleus (see Figure 3B and C).

Impact of Time since Stroke and Lesion Size

Correlation analyses were conducted between time since stroke and the six different learning scores. These analyses showed that time since stroke was not significantly correlated with any of the six learning scores (i.e., SS-TS, SS-TR, SR-TS respectively for Day 1 and Day 2; all with $p \geq .084$), indicating that in the current patient sample time since stroke did not significantly impact on motor sequence learning.

In addition, we examined the impact of lesion size on motor sequence learning. Again no significant association between size of the lesion and magnitude of any of the learning effects was observed (all with $p \geq .079$). Moreover, we examined whether patients with lesions involving the striatum had just bigger lesions than those without striatal involvement by directly comparing the lesion sizes between these two groups (patients with

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021

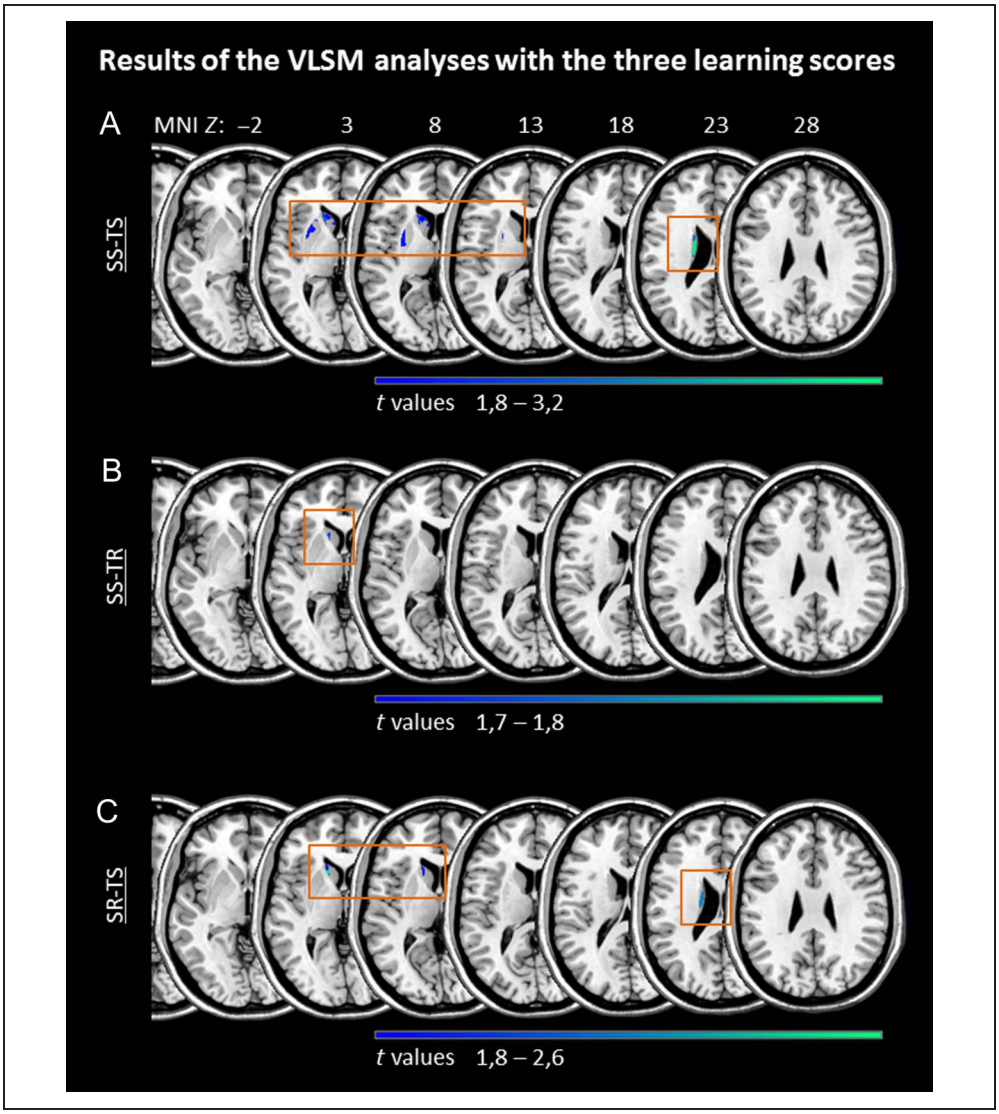

Figure 3. Results of the VLSM analyses. VLSMs were calculated for the three different learning scores on Day 2 (i.e., SS-TS, SS-TR, SR-TS). Diminished learning scores in the SS-TS condition were associated with lesions of the putamen and caudate nucleus (A), whereas diminished learning scores in the learning probes maintaining only one type of sequence information (i.e., SS-TR and SR-TS) were associated with lesions of the caudate nucleus only (B, C). Results are shown on axial slices from MNI *z*-coordinates −2 to 28, at a statistical threshold of $p < .05$ (FDR-corrected, with a cluster threshold of 5 voxels). SS = spatially structured; SR = spatially random; TS = temporally structured; TR = temporally random.

striatal involvement [$n = 13$] vs. patients without striatal involvement [$n = 9$]). An independent two-sample t test with lesion size (number of voxels affected) as dependent variable showed that there was no difference of lesion size between the two patient groups ($t(20) = 0.722$, $p = .479$). This analysis ensured that the current finding of an association between striatal lesions and a decrement in motor learning was not caused by the fact that patients with a striatal involvement had bigger lesions than those without striatal involvement.

DISCUSSION

Skillfully performing complex actions requires the integration of spatial and temporal information about single action elements. Using a specifically designed SRT task (Shin & Ivry, 2002), we investigated whether LH stroke patients were able to concurrently learn spatial and temporal aspects of a complex motor sequence and whether this knowledge could be retrieved after 24 hr. We observed that LH stroke patients were able to learn, retain (over at least 24 hr), and retrieve complex spatiotemporal sequence patterns. Learning of complex spatiotemporal motor sequences is more difficult than learning a spatial sequence with a fixed RSI as variable RSIs result in a higher uncertainty. The learning effect for the combined spatiotemporal sequence was equally large in LH stroke patients and controls on both days. However, although LH stroke patients showed no independent spatial and independent temporal sequence learning on both days, control participants showed significant independent spatial learning on both days and significant independent temporal learning on Day 2. However, differences between the two groups were significant on Day 2 only. The finding that healthy participants showed no (independent) temporal learning on Day 1 is in agreement with the findings by Shin and Ivry (2002), who did not observe independent temporal learning in their healthy participants who were examined on one day only. Our

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021

current study design including an additional assessment on the next day enabled us to show that healthy controls exhibited a significant temporal learning effect on Day 2, indicating that (independent) temporal learning might require more time and/or memory consolidation to emerge. Finally, VLSM analyses revealed that on Day 2 diminished learning effects in all three learning probes were associated with striatal lesions.

In the current study, we used an SRT task in which spatial and temporal sequence information was learned concurrently, because to perform a complex action fluently, the correct order and timing of the single action components is mandatory. Moreover, several studies support the hypothesis that timing is an integral rather than an independent part of motor program representations (Summers, 1975, 1977). Furthermore, Shin and Ivry (2002) reported that significant temporal sequence learning was found only when the temporal sequence was correlated with the spatial sequence during the learning phase (Shin & Ivry, 2002).

Although LH stroke patients showed a combined spatiotemporal learning effect that was comparable to that observed in controls, LH stroke patients did not show learning effects for the learning probes in which only one type of sequence information was maintained whereas the other one was randomized (i.e., SS-TR and SR-TS). Particularly on Day 2, LH stroke patients showed significantly smaller learning scores for these two learning probes. The finding that the LH stroke patients show a learning effect for the combined spatiotemporal sequence but neither for the isolated spatial nor isolated temporal sequence suggests that learning of the integrated spatial and temporal sequence might reflect a third type of sequence learning called relational sequence learning. It is assumed (Shin & Ivry, 2002) that the three types of learning (learning of the spatial sequence, learning of the temporal sequence, and relational learning) additively contribute to the learning effect for the combined spatiotemporal sequence (measured by comparing SS-TS and SR-TR blocks). The fact that patients showed a learning effect for the combined spatiotemporal sequence but not for the isolated spatial and temporal ones supports the notion that relational sequence learning is more than simply the sum of spatial and temporal sequence learning, a notion which has already been put forward by Shin and Ivry (2002). The current data appear to be consistent with this notion as a significant interaction for the variables spatial and temporal structure was revealed, pointing to an overadditive effect of these two variables. Thus, LH stroke patients seem to specifically benefit from this overadditive interaction during combined spatiotemporal sequence learning and therefore show relational but neither isolated spatial nor isolated temporal sequence learning. Given these results and given that the three different aspects of sequence learning (spatial, temporal, and relational) jointly contribute to the combined spatiotemporal learning effect, it is likely that the proportion of the combined spatiotemporal learning effect reflecting relational learning is greater for LH stroke patients than for controls. This is in line with results by Shin, Aparicio, and Ivry (2005), who also reported greater relational learning in patients with unilateral BG lesions as measured by a phase-shift probe in which patients showed greater RT costs than control participants (Shin et al., 2005). A phase-shift block is a block containing both the spatial and temporal sequence information learnt during the learning phase with the only difference that spatial and temporal sequence are no longer correlated but shifted compared to the learning phase. Hence, as both spatial and temporal sequence information are comprised, RT costs in the phase shift block are indicative of relational learning. Although clearly demonstrating relational learning in patients, the conclusion that relational learning is smaller in healthy controls has to be taken with caution. An alternative explanation for the lower RT costs in healthy controls could be that controls formed, next to the combined spatiotemporal sequence, independent spatial and temporal sequence representations, allowing them to respond faster in the transfer blocks where the relational information was missing. Therefore, future studies investigating whether the smaller RT costs in healthy controls indeed reflect a smaller relational learning effect or whether relational learning in controls is similar to that in patients but does not result in large RT costs in phase-shift probes because healthy controls are able to compensate for the missing relational information by the formation of independent sequence representations would be informative.

The finding that LH stroke patients did not show a learning effect for the isolated spatial sequence (i.e., no RT advantage for the SS-TR block) may, at first glance, seem surprising given that previous studies reported preserved spatial sequence learning in patients with LH stroke (Dovern et al., 2011; Boyd et al., 2007; Pohl & McDowd, 2006). However, these studies used fixed (or no) RSIs, which has a predictive value as well, resulting in a condition comparable to our combined spatiotemporal sequence condition (SS-TS) for which LH stroke patients showed an RT advantage. Therefore, we suggest that LH stroke patients rely on multimodal information (here: temporal and spatial information) when retrieving motor sequence knowledge and are very sensitive to any disruption of the initially learnt relational sequence information. That is, our sample of LH stroke patients was indeed able to learn a complex spatiotemporal sequence as well as healthy control participants, but their mental representation of the sequence was more fragile, leading to performance decrements in consequence of any disruptions of the context in which the learnt sequence knowledge had to be retrieved. We suggest that patients formed very rigid/inflexible chunks, whereas healthy controls formed more flexible (higher-order) chunks that they could also access when one sequence dimension was disrupted. For example, when only the temporal structure was modified (e.g., by randomizing the RSIs), but the

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021

spatial sequence information was maintained, the sequence organization was completely disrupted in patients, whereas controls were still able to anticipate the upcoming stimulus location and thus showed an RT benefit. Thus, it is likely that controls formed higher-order chunks and were thereby able to access the learnt sequence information by focusing either on the target location where or the point in time when the next stimulus appeared, thereby allowing for response preparatory processes and faster responses (Coull, 2004; Coull & Nobre, 1998; Posner, 1980). An alternative explanation could be that healthy controls formed, in addition to the integrated spatiotemporal sequence representation, independent representations of the pure spatial and the pure temporal sequence by disintegrating this information from the combined spatiotemporal sequence information whereas patients did not form those independent sequence representations. The two explanations for the differences observed between the LH patient group and the control group are not mutually exclusive, because generating flexible chunks would actually facilitate the formation of independent spatial or temporal representations.

Contrary to our initial hypotheses, statistical lesion analyses using VLSM did not reveal a significant association between lesions of the (left) IPC and any of the learning scores. Because LH stroke patients showed intact spatiotemporal integration, this finding most likely reflects the patients' sustained ability to make use of implicit timing as revealed by clear RT advantages in the combined spatiotemporal sequence condition. Furthermore, particular task specifications may account for this finding. A meta-analysis of neuroimaging studies of temporal processing showed that different neural networks were recruited for tasks in which timing is performed automatically and for timing tasks that require more cognitive control. Tasks in which timed responses are performed rather automatically recruit a motor network including striatum, cerebellum, and SMA. In contrast, the parietal cortex is specifically recruited for cognitively more demanding timing tasks (Lewis & Miall, 2003). In the current version of the SRT task, the responses are given in a continuous rhythmical pattern based on the temporal sequence. Therefore, the timed responses were given rather automatically in the current experimental paradigm. This was also indicated by the fact that participants were not able to explicitly retrieve the temporal sequence afterward. Thus, it is likely that we did not observe any relevant parietal involvement as the current SRT task was based on automatic rather than cognitive demanding timing.

In contrast, the ROI analyses of the striatum revealed that diminished learning scores of all three learning probes on Day 2 were associated with lesions of the striatum. The striatum has been shown to play a critical role in motor chunking, a process linking multiple movements into groups, thereby forming single motor units (Penhune & Steele, 2012; Orban et al., 2011; Graybiel, 1998, 2008). Hence, the fact that striatal lesions were associated with reduced learning scores for all three learning probes on Day 2 is in line with the idea that chunking underlies the formation of independent spatial and temporal sequence representations as also the SS-TS probe does not only comprise relational but also independent sequence learning as discussed above. Moreover, differences between LH stroke patients and healthy controls emerged on Day 2 only, suggesting that offline consolidation was impaired in stroke patients. This is also in agreement with previous studies showing that the striatum is specifically involved in the late encoding phase of motor sequence learning (Seidler et al., 2005) and in offline procedural memory consolidation (Debas et al., 2010, 2014; Albouy et al., 2008). In addition, the striatum was also shown to be critically involved in the overnight consolidation of a temporal rhythm in a rhythmical finger tapping task (Lewis, Couch, & Walker, 2011).

Our results may seem to be at odds with findings reported by Shin and colleagues (2005) who applied the same task to four patients with focal BG lesions and reported that these patients learned both the spatial and temporal sequences independently (Shin et al., 2005). Shin and colleagues defined the learning effect as an RT disadvantage compared with the RT in blocks comprising both the spatial and temporal sequences (e.g., SS-TR minus SS-TS being indicative of temporal learning). In contrast, we defined the learning effect as an RT advantage compared to the RT in the block comprising randomized sequences only (e.g., SR-TR minus SR-TS being indicative of temporal learning). Note that larger RT costs in the timing probe used by Shin and colleagues (2005) are not necessarily indicative of temporal sequence learning but could also result from a failure to develop a separable representation of the spatial sequence. This alternative interpretation of their results can also explain the puzzling finding that the temporal learning effect was even larger in their patients than in their controls: the smaller RT costs for the temporal learning probe (SS-TR minus SS-TS) in controls could also result from the healthy controls' ability to develop an independent representation of the spatial sequence, thereby enabling them to respond faster in the transfer block (SS-TR). In the current study, we were able to replicate the results by Shin and colleagues (2005) when analyzing RT costs (i.e., defining the learning score for temporal learning as the RT increase in the SS-TR block compared to the SS-TS blocks): that is, LH stroke patients showed larger RT costs (22 and 21 msec on Day 1 and Day 2, respectively) than healthy controls (14 and 4 msec on Day 1 and Day 2, respectively). However, as control participants responded faster (i.e., showed less RT costs) than patients, an alternative interpretation to the interpretation that the higher RT costs reflect a better temporal learning effect in patients should be considered: The faster RTs (and thus lower RT costs) in control participants in the SS-TR block could also result from the fact that controls (but not [LH stroke] patients) are—despite

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021

randomized RSIs—able to make use of the spatial information (i.e., anticipating where the next stimulus will appear) allowing for better response preparatory processes. Therefore, we suggest that to assess isolated temporal sequence learning it is advisable to look at the RT advantages in the SR-TS block compared to the completely randomized block (i.e., randomized with respect to both the temporal and the spatial sequence [SR-TR]). Here, RT advantages can only emerge if a participant has built some independent temporal sequence knowledge. Taken together, the current findings in LH stroke patients do not contradict those by Shin and colleagues (2005). In fact, we were able to replicate their findings (in patients with BG lesions). Moreover, we were able to extend their findings by including a block with completely randomized sequences (SR-TR). This enabled us to analyze the RT data in a different way leading to an alternative interpretation and providing an explanation for the puzzling finding that patients appear to show a bigger temporal learning effect than control participants when the analysis focuses on RT costs.

Finally, some limitations of the current study need to be acknowledged. One potential limitation concerns the healthy control participants. No structural imaging data were acquired for the healthy controls to check for brain lesions, for example, due to degenerative or vascular disease. Especially, with respect to the striatum, it has been demonstrated that neuronal degeneration occurs with increasing age also in healthy participants (Haycock et al., 2003). With respect to vascular accidents (stroke or TIA), a structured interview was conducted to carefully screen participants for any symptoms of a TIA or stroke. Although we are aware of the limited reliability of self-reports, this procedure considerably increases the likelihood of uncovering previous cerebrovascular accidents.

With respect to the clinical implications of the current study, it is of note that the current patients with a wide range of stroke severity were able to learn and retain motor sequences when both spatial and temporal information was available. Findings by Boyd and colleagues that stroke severity impacts on implicit motor learning may suggest that stroke severity needs to be considered in the analyses (Boyd et al., 2007). However, the association between stroke severity and motor sequence learning critically depends on the task complexity. That is, although severely affected stroke patients performed worse in a serial hand movement task, in which responses require different hand postures, they showed no decrement of the learning effect in an SRT task requiring simple button presses (Boyd et al., 2007). Therefore, behavioral deficits in the current study are likely to be attributed to the specific task characteristics (i.e., the new temporal aspect) rather than to stroke severity in general. Consistent with this notion we also did not observe any association between lesion size and the different learning scores.

Conclusions with respect to a hemispheric specificity of our findings have to be taken with caution as no patients with right hemispheric stroke were included in the current study. We focused on patients with LH stroke as temporal processing is primarily a function of the left hemisphere (Wiener et al., 2010; Lux, Marshall, Ritzl, Zilles, & Fink, 2003). Further studies are required to examine whether findings of the current study are specific for patients with LH stroke or also transferable to patients with right-hemispheric stroke. The finding that lesions of the left striatum were associated with deficits in all three learning probes implicates that motor chunking is the underlying core process (Penhune & Steele, 2012). Moreover, the association between striatal lesions and motor learning deficits on Day 2 suggest that offline consolidation processes may be disturbed in LH stroke patients (Debas et al., 2010, 2014; Albouy et al., 2008). However, systematic studies in patients with unilateral as well as bilateral focal lesions of the striatum are warranted to further differentiate the role of the (left and right) striatum in these processes.

In conclusion, our study shows that patients with an LH stroke were able to learn complex spatiotemporal motor sequences and that they were able to retrieve this spatiotemporal sequence knowledge even after 24 hr. These findings are of particular interest for rehabilitation after stroke, where motor learning is of particular importance when reacquiring motor skills. However, in our sample of LH stroke patients, the sequence representations were very fragile and sensitive to any disruptions of the context. That is, in blocks where only one type of sequence information (i.e., spatial or temporal) was maintained while the other one was randomized, patients failed to show a significant RT benefit. This effect was specifically pronounced on Day 2, where patients showed significantly smaller learning scores on these learning probes compared with controls. The data indicate that our LH stroke patients were more dependent on multimodal sequence information (here spatial and temporal sequence information) and that in patients motor sequence learning was context dependent and that they showed little transfer of learned motor sequence knowledge (i.e., patients retrieved motor sequence knowledge only under conditions identical to those of the learning phase). VLSM analyses showed that on Day 2 diminished learning scores of all three learning probes (SS-TS, SS-TR, SR-TS) were associated with striatal lesions. This might be attributed to its role in motor chunking or offline consolidation, as group differences occurred on Day 2 only.

Acknowledgments

G. R. F. gratefully acknowledges support from the Marga and Walter Boll Foundation. D. C. T. and P. H. W. are supported by the German-Israel Foundation (GIF I-1110-93.4/2010).

Reprint requests should be sent to Dr. Anna Dovern, Cognitive Neuroscience, Institute of Neuroscience and Medicine (INM-3), Research Center Jülich, Leo-Brandt-Str. 5, 52425 Jülich, Germany, or via e-mail: a.dovern@fz-juelich.de.

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021

REFERENCES

Albouy, G., Sterpenich, V., Balteau, E., Vandewalle, G., Desseilles, M., Dang-Vu, T., et al. (2008). Both the hippocampus and striatum are involved in consolidation of motor sequence memory. *Neuron, 58,* 261–272.

Assmus, A., Marshall, J. C., Noth, J., Zilles, K., & Fink, G. R. (2005). Difficulty of perceptual spatiotemporal integration modulates the neural activity of left inferior parietal cortex. *Neuroscience, 132,* 923–927.

Assmus, A., Marshall, J. C., Ritzl, A., Zilles, K., Noth, J., & Fink, G. R. (2003). Left inferior parietal cortex integrates time and space during collision judgements. *Neuroimage, 20,* S82–S88.

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., et al. (2003). Voxel-based lesion-symptom mapping. *Nature Neuroscience, 6,* 448–450.

Boyd, L. A., Quaney, B. M., Pohl, P. S., & Winstein, C. J. (2007). Learning implicitly: Effects of task and severity after stroke. *Neurorehabilitation and Neural Repair, 5,* 444–454.

Boyd, L. A., & Winstein, C. J. (2001). Implicit motor-sequence learning in humans following unilateral stroke: The impact of practice and explicit knowledge. *Neuroscience Letters, 298,* 65–69.

Cohen, A., Ivry, R. I., & Keele, S. W. (1990). Attention and structure in sequence learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 16,* 17–30.

Cotti, J., Rohenkohl, G., Stokes, M., Nobre, A. C., & Coull, J. T. (2011). Functionally dissociating temporal and motor components of response preparation in left intraparietal sulcus. *Neuroimage, 54,* 1221–1230.

Coull, J. T. (2004). fMRI studies of temporal attention: Allocating attention within, or towards, time. *Cognitive Brain Research, 21,* 216–226.

Coull, J. T., Davranche, K., Nazarian, B., & Vidal, F. (2013). Functional anatomy of timing differs for production versus prediction of time intervals. *Neuropsychologia, 51,* 309–319.

Coull, J. T., & Nobre, A. C. (1998). Where and when to pay attention: The neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI. *Journal of Neuroscience, 18,* 7426–7435.

Daselaar, S. M., Rombouts, S. A., Veltman, D. J., Raaijmakers, J. G., & Jonker, C. (2003). Similar network activated by young and old adults during the acquisition of a motor sequence. *Neurobiology of Aging, 24,* 1013–1019.

Davranche, K., Nazarian, B., Vidal, F., & Coull, J. (2011). Orienting attention in time activates left intraparietal sulcus for both perceptual and motor task goals. *Journal of Cognitive Neuroscience, 23,* 3318–3330.

De Renzi, E., Pieczuro, A., & Vignolo, L. A. (1968). Ideational apraxia: A quantitative study. *Neuropsychologia, 6,* 41–52.

Debas, K., Carrier, J., Barakat, M., Marrelec, G., Bellec, P., Abdallah, H. T., et al. (2014). Off-line consolidation of motor sequence learning results in greater integration within a cortico-striatal functional network. *Neuroimage, 99,* 50–58.

Debas, K., Carrier, J., Orban, P., Barakat, M., Lungu, O., Vandewalle, G., et al. (2010). Brain plasticity related to the consolidation of motor sequence learning and motor adaptation. *Proceedings of the National Academy of Sciences, U.S.A., 107,* 17839–17844.

Dovern, A., Fink, G. R., Saliger, J., Karbe, H., Koch, I., & Weiss, P. H. (2011). Apraxia impairs intentional retrieval of incidentally acquired motor knowledge. *Journal of Neuroscience, 31,* 8102–8108.

Eickhoff, S., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., et al. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage, 25,* 1325–1335.

Goldenberg, G. (1996). Defective imitation of gestures in patients with damage in the left or right hemispheres. *Journal of Neurology, Neurosurgery, and Psychiatry, 61,* 176–180.

Graybiel, A. M. (1998). The basal ganglia and chunking of action repertoires. *Neurobiology of Learning and Memory, 70,* 119–136.

Graybiel, A. M. (2008). Habits, rituals, and the evaluative brain. *Annual Review of Neuroscience, 31,* 359–387.

Haycock, J. W., Becker, L., Ang, L., Furukawa, Y., Hornykiewicz, O., & Kish, S. J. (2003). Marked disparity between age–related changes in dopamine and other presynaptic dopaminergic markers in human striatum. *Journal of Neurochemistry, 87,* 574–585.

Hazeltine, E., Grafton, S. T., & Ivry, R. B. (1997). Attention and stimulus characteristics determine the locus of motor-sequence encoding. A PET study. *Brain, 120,* 123–140.

Hesse, M. D., Thiel, C. M., Stephan, K. E., & Fink, G. R. (2006). The left parietal cortex and motor intention: An event-related functional magnetic resonance imaging study. *Neuroscience, 140,* 1209–1221.

Hoffmann, J., & Koch, I. (1998). Implicit learning of loosely defined structures. In M. A. Stadler & P. A. Frensch (Eds.), *Handbook of implicit learning* (pp. 161–199). Thousand Oaks, CA: SAGE Publications, Inc.

Kalbe, E., Reinhold, N., Brand, M., Markowitsch, H. J., & Kessler, J. (2005). A new test battery to assess aphasic disturbances and associated cognitive dysfunctions—German normative data on the aphasia check list. *Journal of Clinical and Experimental Neuropsychology, 27,* 779–794.

Koch, I. (2007). Anticipatory response control in motor sequence learning: Evidence from stimulus–response compatibility. *Human Movement Science, 26,* 257–274.

Koch, I., & Hoffmann, J. (2000). Patterns, chunks, and hierarchies in serial reaction-time tasks. *Psychological Research, 63,* 22–35.

Lewis, P. A., Couch, T. J., & Walker, M. P. (2011). Keeping time in your sleep: Overnight consolidation of temporal rhythm. *Neuropsychologia, 49,* 115–123.

Lewis, P. A., & Miall, R. C. (2003). Distinct systems for automatic and cognitively controlled time measurement: Evidence from neuroimaging. *Current Opinion in Neurobiology, 13,* 250–255.

Lux, S., Marshall, J. C., Ritzl, A., Zilles, K., & Fink, G. R. (2003). Neural mechanisms associated with attention to temporal synchrony versus spatial orientation: An fMRI study. *Neuroimage, 20,* S58–S65.

Lyle, R. C. (1981). A performance test for assessment of upper limb function in physical rehabilitation treatment and research. *International Journal of Rehabilitation Research, 4,* 483–492.

Medical Research Council of the United Kingdom. (1978). *Aids to examination of the peripheral nervous system: Memorandum no 45.* Palo Alto, CA: Pedragon House.

Nissen, M. J., & Bullemer, P. (1987). Attentional requirements of learning: Evidence from performance measures. *Cognitive Psychology, 19,* 1–32.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9,* 97–113.

Orban, P., Peigneux, P., Lungu, O., Debas, K., Barakat, M., Bellec, P., et al. (2011). Functional neuroanatomy associated with the expression of distinct movement kinematics in motor sequence learning. *Neuroscience, 179,* 94–103.

Orrell, A. J., Eves, F. F., Masters, R. S. W., & MacMahon, K. M. M. (2007). Implicit sequence learning processes after unilateral stroke. *Neuropsychological Rehabilitation, 17,* 335–354.

Peigneux, P., Maquet, P., Meulemans, T., Destrebecqz, A., Laureys, S., Degueldre, C., et al. (2000). Striatum forever,

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021

despite sequence learning variability: A random effect analysis of PET data. *Human Brain Mapping, 10,* 179–194.
Penhune, V. B., & Steele, C. J. (2012). Parallel contributions of cerebellar, striatal and M1 mechanisms to motor sequence learning. *Behavioural Brain Research, 226,* 579–591.
Pohl, P. S., & McDowd, J. M. (2006). Implicit learning of a motor skill after mild and moderate stroke. *Clinical Rehabilitation, 20,* 246–253.
Pohl, P. S., McDowd, J. M., Filion, D. L., Richards, L. G., & Stiers, W. (2001). Implicit learning of a perceptual-motor skill after stroke. *Physical Therapy, 81,* 1780–1789.
Posner, M. I. (1980). Orienting of attention. *Quarterly Journal of Experimental Psychology, 32,* 3–25.
Rankin, J. (1957). Cerebral vascular accidents in patients over the age of 60: II. Prognosis. *Scottish Medical Journal, 2,* 200–215.
Reed, J., & Johnson, P. (1994). Assessing implicit learning with indirect tests: Determining what is learned about sequence structure. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 20,* 585–594.
Reiss, J. P., Campbell, D. W., Leslie, W. D., Paulus, M. P., Stroman, P. W., Polimeni, J. O., et al. (2005). The role of the striatum in implicit learning: A functional magnetic resonance imaging study. *NeuroReport, 16,* 1291–1295.
Rieckmann, A., Fischer, H., & Bäckman, L. (2010). Activation in striatum and medial temporal lobe during sequence learning in younger and older adults: Relations to performance. *Neuroimage, 50,* 1303–1312.
Rorden, C., Karnath, H.-O., & Bonilha, L. (2007). Improving lesion-symptom mapping. *Journal of Cognitive Neuroscience, 19,* 1081–1088.
Rushworth, M. F. S., Krams, M., & Passingham, R. E. (2001). The attentional role of the left parietal cortex: The distinct lateralization and localisation of motor attention in the human brain. *Journal of Cognitive Neuroscience, 13,* 698–710.
Sakai, K., Kitaguchi, K., & Hikosaka, O. (2003). Chunking during human visuomotor sequence learning. *Experimental Brain Research, 152,* 229–242.
Schellig, D. (1997). *Block-Tapping-Test*. Frankfurt, Germany: Swets Test Services GmbH.
Schwarb, H., & Schumacher, E. H. (2012). Generalized lessons about sequence learning from the study of the serial reaction time task. *Advances in Cognitive Psychology, 8,* 165.
Seashore, C. E., Lewis, D., & Saetveit, J. G. (1960). *Seashore measures of musical talents*. New York: The Psychological Corporation.
Seidler, R. D., Purushotham, A., Kim, S. G., Ugurbil, K., Willingham, D., & Ashe, J. (2005). Neural correlates of encoding and expression in implicit sequence learning. *Experimental Brain Research, 165,* 114–124.
Shin, J. C., Aparicio, P., & Ivry, R. B. (2005). Multidimensional sequence learning in patients with focal basal ganglia lesions. *Brain and Cognition, 58,* 75–83.
Shin, J. C., & Ivry, R. B. (2002). Concurrent learning of temporal and spatial sequences. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 28,* 445–457.
Spreen, O., & Strauss, E. (1991). *A compendium of neuropsychological tests*. New York: Oxford University Press.
Stadler, M. A. (1993). Implicit serial learning: Questions inspired by Hebb (1961). *Memory & Cognition, 21,* 819–827.
Summers, J. J. (1975). The role of timing in motor program representation. *Journal of Motor Behavior, 7,* 229–241.
Summers, J. J. (1977). The relationship between the sequencing and timing components of a skill. *Journal of Motor Behavior, 9,* 49–59.
Thoenissen, D., Zilles, K., & Toni, I. (2002). Differential involvement of parietal and precentral regions in movement preparation and motor intention. *Journal of Neuroscience, 22,* 9024–9034.
Weiss, P. H., Kalbe, E., Kessler, J., & Fink, G. R. (2013). *Kölner Apraxie-Screening*. Göttingen, Germany: Hogrefe Verlag.
Wiener, M., Turkeltaub, P. E., & Coslett, H. (2010). Implicit timing activates the left inferior parietal cortex. *Neuropsychologia, 48,* 3967–3971.

Downloaded from http://direct.mit.edu/jocn/article-pdf/28/2/223/1784298/jocn_a_00890.pdf by guest on 25 June 2021