Neuropsychologia 159 (2021) 107921

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Motor sequence learning in patients with ideomotor apraxia: Effects of long-term training

Sarah Willms [a], Miriam Abel [a], Avi Karni [b], Carmit Gal [b], Julien Doyon [c], Bradley R. King [d,e], Joseph Classen [f], Jost-Julian Rumpf [f], Giovanni Buccino [g], Antonello Pellicano [a], Juliane Klann [a,h], Ferdinand Binkofski [a,i,*]

[a] Division for Clinical and Cognitive Sciences, Department of Neurology, Medical Faculty, RWTH Aachen University, Germany
[b] Department of Neurobiology, University of Haifa, Israel
[c] McConnell Brain Imaging Centre, McGill University, Montreal, Canada
[d] Department of Health and Kinesiology, University of Utah, USA
[e] Department of Movement Sciences, KU Leuven, Belgium
[f] Department of Neurology, University of Leipzig, Germany
[g] Division of Neuroscience, IRCCS San Raffaele and Vita Salute San Raffaele University, Milano, Italy
[h] SRH University of Applied Health Sciences, Campus Heidelberg, Germany
[i] Institute for Medicine and Neuroscience (INM-4), Research Center Jülich GmbH, Germany

ARTICLE INFO

Keywords:
Apraxia
chronic stroke
motor sequence learning
long term training
motor memory

ABSTRACT

Recent studies show that limb apraxia is a quite frequent, yet often underdiagnosed, higher motor impairment following stroke. Because it adversely affects every-day life and personal independence, successful rehabilitation of apraxia is essential for personal well-being. Nevertheless, evidence of long-term efficacy of training schemes and generalization to untrained actions is still scarce. One possible reason for the tendency of this neurological disorder to persist may be a deficit in planning, conceptualisation and storage of complex motor acts.

This pilot study aims at investigating explicit motor learning in apractic stroke patients. In particular, we addressed the ability of apractic patients to learn and to retain new explicit sequential finger movements across 10 training sessions over a 3-week interval.

Nine stroke patients with ideomotor apraxia in its chronic stage participated in a multi-session training regimen and were included in data analyses. Patients performed an explicit finger sequence learning task (MSLT – motor sequence learning task), which is a well-established paradigm to investigate motor learning and memory processes.

Patients improved task performance in terms of speed and accuracy across sessions. Specifically, they showed a noticeable reduction in the mean time needed to perform a correct sequence and the number of erroneous sequences. We found also a trend for improved performance at the Goldenberg apraxia test protocol: "imitation of meaningless hand and finger gestures" relative to when assessed before the MSLT training.

Patients with ideomotor apraxia demonstrated the ability to acquire and maintain a novel sequence of movements; and, this training was associated with hints towards improvement of apraxia symptoms.

1. Introduction

Limb apraxia is a higher cognitive motor deficit mainly due to left hemispheric stroke and affecting both sides of the body (Goldenberg, 2009, 2013, 2015, 2015). Frequent clinical symptoms of apraxia are deficits in 1) the imitation of meaningless gestures, 2) pantomiming the use of objects and tools, and 3) actual tool use (Dovern et al., 2011; Goldenberg, 2009, 2013). Deficits of imitation and pantomime fit more or less to the ideomotor apraxia as defined by Liepmann (1920).

Ideomotor apraxia symptoms occur most frequently after lesions in different left hemispheric fronto-parietal brain areas. The literature, however, is heterogeneous with respect to the relation between symptoms and lesion site (Buxbaum and Randerath, 2018). Previous studies have suggested that the different symptoms rely on different neural

* Corresponding author. Division for Clinical Cognitive Sciences Medical Faculty, RWTH Aachen University, Pauwelsstrasse 1, 52074, Aachen, Germany.
E-mail address: fbinofski@ukaachen.de (F. Binkofski).

https://doi.org/10.1016/j.neuropsychologia.2021.107921
Received 20 November 2020; Received in revised form 10 June 2021; Accepted 18 June 2021
Available online 25 June 2021

structures (Goldenberg et al., 2007). Impaired imitation of hand postures is a result of lesions of the inferior parietal lobule, the medial temporal gyrus, and the medial occipital gyrus of the left hemisphere (Goldenberg and Karnath, 2006). Deficient imitation of finger postures is caused by lesions of the frontal areas, in the inferior frontal gyrus, the nucleus caudatus, the putamen and the insula (Mühlau et al., 2005). In sum, this body of evidence suggests an essential function of the inferior parietal cortex for imitation (Ant et al., 2019; Mengotti et al., 2013; Niessen et al., 2014; Rumiati et al., 2010). Deficits in pantomime of object use are strictly bound to inferior left hemisphere lesions (Goldenberg et al., 2007). Further studies found that the left inferior parietal cortex, including the inferior parietal lobe (IPL), plays a key role in the context of pantomime of object use (Niessen et al., 2014; Weiss et al., 2014). However, the inferior frontal and precentral areas are also important (Goldenberg et al., 2007; Mühlau et al., 2005; Weiss et al., 2014). Goldenberg and Spatt (2009) reported that lesions of inferior parietal and precentral areas, and of the middle temporal gyrus impair the actual tool use.

Altogether, these results provide some evidence that ideomotor apraxia originates from lesions of the ventro-dorsal stream areas with mostly preserved dorso-dorsal stream areas (Binkofski and Fink, 2005; Binkofski and Buxbaum, 2013; Binkofski, 2020).

In addition to aphasia, ideomotor apraxia is one of the most common and persistent impairments following stroke and adversely affects activities of daily, as well as professional life (Goldenberg and Spatt, 2009). Success in rehabilitation of apraxia seems to be limited: Patients with apraxia often demonstrate poor, short lasting, and item specific benefits, as well as poor transfer effects to untrained actions from motor therapy (Binkofski and Klann, 2013; Dovern et al., 2011; Heilman et al., 1975; Motomura et al., 1989; Rothi and Heilman, 1984; (see also Pérez-Mármol et al., 2015; for a protocol of a clinical trial based on physical and occupational therapy for limb apraxia). This leads frequently to an increasing dependence on the support by caregivers even after discharge from rehabilitation (Niessen et al., 2014).

Since the recovery of praxis may be conceptualized as a process, the persistence of apractic symptoms raises the question as to whether these patients still exhibit the capacity to learn novel motor skills (Dovern et al., 2011; Seitz, 2001). Patients with limb apraxia have shown evidence of short-term implicit motor learning (Dovern et al., 2011); but whether they can learn and retain new explicit motor sequences, as learned in several sessions, is still an unresolved question.

A well-established paradigm to examine the acquisition and retention of motor memories is the *motor sequence learning task* (MSLT; e.g., Doyon and Ungerleider et al., 2002; Doyon et al., 2009): a simple finger-tapping task similar to the classical finger opposition sequence (FOS; e.g. Karni, 1995). Frequent training at this task results in a faster, more accurate and effortless performance of finger movements. Such behavioral gains appear during active task practice (i.e., online) as well as during intervals of non-practice between task sessions (i.e., offline) (Doyon et al., 2009, 2018; Karni et al., 1995; Dahms et al., 2019). These offline performance enhancements, along with reduced susceptibility to interfering experiences, are considered markers of the motor memory consolidation process during which initially labile memory traces are transformed into a more stable, robust form. Important in the context of the current research, healthy older adults have demonstrated the ability to learn and consolidate a new sequence of finger movements, although the consolidation process does appear to be degraded with age (King et al., 2013; Gal et al., 2019).

Acquisition of motor skills is viewed today as a staged process that follows three distinct phases (Censor et al., 2012; Doyon et al., 2009; King et al., 2013; Lehéricy et al., 2005; Dahms et al., 2019). In a short initial acquisition phase, behavioral gains appear rapidly within the session (i.e., on-line). In a slow, across session retention process, smaller improvements induced by repeated training extend over a longer period of time from days to months. Between training sessions, an intermediate consolidation phase is situated in which the motor memory undergoes "off-line" transformations with sleep playing a very important role in this process (Albouy et al., 2013). Indeed, the initially labile motor memory trace is transformed in a more stable and resistant form (Korman et al., 2007; Krakauer and Shadmehr, 2006; Walker et al., 2003; Laventure et al., 2018; Dahms et al., 2019).

MSLT studies conducted on patients aimed (i) to evaluate the functional impairment of the motor system (after damage to the cortico-striatal and cortico-cerebellar circuitry), and (ii) to assess the impact of clinical interventions on motor learning capacity.

In sum, ideomotor apraxia is characterized by impaired execution of already learned complex actions on both sides of the body as a consequence of lesions in the left hemisphere, despite preserved basic motor and sensory functions. In the present pilot study, we explored whether and to what extent the explicit learning of a new action, in the form of a complex movement pattern, is possible in such persons who have deficits in complex motor abilities and would not be able develop (or could hardly develop) new ones. We moved from the assumption that the to-be-learned action, on the one hand, and the impaired actions, on the other hand, share a common explicit learning component. Consequently, we investigated a possible relationship between the significant acquisition of new motor abilities in patients with ideomotor apraxia and the severity of their impaired motor activities, before and after the motor training. Thus, we explored the possibility that the learning of a new motor ability could correspond to some extent to improvements in apraxia deficits.

2. Methods

2.1. Participants

Twelve patients with chronic ideomotor apraxia after left brain ischemic stroke were recruited from the in-house Aphasia ward of the University Hospital of Aachen, relying on the Apraxia screening. Three patients were excluded from final evaluation due to incomplete data. Data of the remaining 9 patients (mean age: 44 years; SD: 11.1; age range: 33–69 years; 4 women) were entered into the data analysis. In addition to the persisting idoemotor apraxia, all patients suffered from aphasia. Furthermore, all patients had right-sided hemiparesis and apraxia of speech. The mean duration since onset of the disease was 28 months post stroke (range 8–76 months). All participants were right-handed based on the Edinburgh Handedness Inventory (Oldfield, 1971). Additional inclusion criteria were the following: 1) at least three months post stroke, 2) ideomotor apraxia according to the Goldenberg protocols on apraxia of upper limbs (Goldenberg, 1996; Goldenberg and Spatt, 2009). Ideomotor apraxia was diagnosed when the patient scored below the cut-off value in at least one of the five Goldenberg protocols (see clinical assessments section; see also Table 1 and Table 2). Patients with clinical signs of depression, anxiety disorder or neglect were not included in the study.

All patients gave their written informed consent prior to the study. Characteristics of all evaluated patients are listed in Table 1. The project was approved by the Ethics Committee of the Medical Faculty at RWTH Aachen University.

2.2. Experimental design

To assess patients' motor learning capabilities, changes in MSLT performance were investigated across and between 10 training sessions. Each session was performed in the evening, since recent evidence has been provided in healthy population of a longer term retention of acquired motor skills in evening as compared to morning training (Gal et al., 2019). Furthermore, to examine potential improvements of apractic symptoms induced by motor training, all five Goldenberg protocols (i.e., G1 to G5) were administered to patients before and after the 10 motor training sessions (see Clinical assessments section).

Table 1
Demographic and clinical data of our patients with apraxia. (F) female, (M) male, (–) severe impairment, (−) moderate impairment, (+) not affected. MCA, middle cerebral artery. Hemiparesis was assessed according to MRC (Medical Research Council scale). HD, handedness.

Patient	Gender:	Age (y)	HD	Site of lesion	Duration since onset (months)	Type of apraxia	Other symptoms
P1	M	46	R	ischemic stroke in left MCA territory	18	Imitation (–) Pantomime (−) Object use (+)	Hemiparesis right, moderate Broca aphasia, buccofacial apraxia
P2	M	69	R	ischemic stroke in left MCA territory	27	Imitation (–) Pantomime (–) Object use (+)	Severe Broca aphasia, severe apraxia of speech, buccofacial apraxia
P3	F	33	R	ischemic stroke in left MCA territory	11	Imitation (−) Pantomime (–) Object use (+)	Slight sensorimator hemiparesis right, rest symptoms of aphasia, apraxia of speech,
P4	M	44	R	Ischemic stroke in the basal ganglia left	11	Imitation (–) Pantomime (–) Object use (+)	Hemiparesis right, global aphasia, apraxia of speech, buccofacial apraxia
P5	F	57	R	ischemic stroke in left MCA territory	76	Imitation (−) Pantomime (–) Object use (+)	Slight arm hemiparesis right, global aphasia, apraxia of speech, buccofacial apraxia
P6	M	53	R	ischemic stroke in left MCA territory	13	Imitation (−) Pantomime (−) Object use (+)	Hemiparesis right, severe Broca aphasia, buccofacial apraxia, apraxia if speech
P7	M	63	R	ischemic stroke in left MCA territory	8	Imitation (−) Pantomime (−) Object use (+)	Hemiparesis right, moderate global aphasia, severe apraxia of speech, buccofacial apraxia, facial apraxia
P10	F	53	R	ischemic stroke in left MCA territory	51	Imitation (–) Pantomime (–) Object use (+)	Hemiparesis right, chronic pain disorder, moderate Broca aphasia, apraxia of speech
P12	F	42	R	ischemic stroke in left MCA territory	38	Imitation (–) Pantomime (−) Object use (+)	Hemiparesis right, amnestic aphasia, apraxia of speech

2.3. Clinical assessments

The following standard tests were used to examine the severity of ideomotor apraxia and to control for cognitive, neuropsychological and psychiatric disorders:

The “Albert’s Neglect Test” (line bisection) measured possible neglect (Fullerton et al., 1986). Mean percentage of uncrossed lines for the nine patients was 18%, s.d. = 6.7. As a range of 70–100% represents a neglect diagnosis, no patient showed signs of neglect. Symptoms of depression and anxiety disorders were assessed by the “Beck Depression Inventory (BDI-II)” (Hautzinger et al., 2006) and the “Beck Anxiety Inventory (BAI)” (Margraf and Ehlers, 2007). Patients had a mean BDI of 9,2 (SD: 4,4) and a mean BAI of 8,8 (SD: 3,4), therefore none were considered to have clinical levels of depression or anxiety. To assess the “limb apraxia” inclusion criteria, the Goldenberg Protocols I–V for the three domains of apraxia were used: imitation of meaningless hand postures (G1), imitation of meaningless finger postures (G2), imitation of meaningless hand and finger gestures (G3), pantomime of object use (G4) actual tool use (G5).

2.4. Motor sequence learning task (MSLT)

A well-established MSLT (e.g. Doyon et al., 2009) was implemented that was nearly identical to the version adapted by Gal and colleges (2019). Patients were trained in the University Hospital of Aachen within an ad-hoc training program. They were comfortably seated in front of a computer screen and were instructed to practice a five element finger tapping sequence (excluding the thumb) on a customized, four-button keypad (Belkin Razer Nostromo, Belkin, Playa Vista, USA, see Fig. 1) with their left hand, as rapidly as possible while making as few errors as possible. Prior to the beginning of the training phase, the sequence 4–1 – 3–2 – 4 (1 = index finger, 2 = middle finger, 3 = ring finger, 4 = little finger) was explicitly provided to the patients, who had to perform 3 consecutive sequence repetitions, slowly and without any errors, before the start of the training session (see also King et al., 2017a, 2017b, 2020a; 2020b; Rumpf et al., 2017). The training session encompassed 14 consecutive practice blocks separated by 30-s rest blocks. During practice blocks, a green fixation cross, but no information on the sequence, was displayed on the computer screen. To control for the number of movements, each practice block was terminated after 30 key presses signaled by a colour change of the fixation cross (from green to red) (Fig. 2). Therefore, a maximum of 6 correct sequences could be

Table 2
Individual and group scores for the Goldenberg test protocols assessing apraxia symptoms before and after the motor training. The clinical cut-off scores were as follows: G1 = 19 points, G2 = 19 points, G3 = 19 points, G4 = 51 points, G5 = 19 points. The differences between the scores assessed before and after the motor training were computed for each patient. Patients were then classified as showing improvement (i.e., difference > 0) or no improvement (i.e., difference≤0).

Goldenberg test		Patient	Before		After		Difference	Group
G1	imitation of meaningless hand postures	1	15		16		1	Improve
		2	14		12		−2	No improve
		3	15		20		5	Improve
		4	12		10		−2	No improve
		5	18		18		0	No improve
		6	20		20		0	Ceiling
		7	5		17		12	Improve
		10	14		15		1	Improve
		12	13		15		2	Improve
			Mean	S.D.	Mean	S.D.		
			14.00	4.18	15.89	3.37		
G2	imitation of meaningless finger postures	1	7		16		9	Improve
		2	17		20		3	Improve
		3	19		19		0	No improve
		4	15		14		−1	No improve
		5	19		18		−1	No improve
		6	16		9		−7	No improve
		7	11		15		4	Improve
		10	11		14		3	Improve
		12	15		20		5	Improve
			Mean	S.D.	Mean	S.D.		
			14.44	4.03	16.11	3.59		
G3	imitation of meaningless hand and finger gestures	1	3		1		−2	No improve
		2	9		7		−2	No improve
		3	12		15		3	Improve
		4	6		9		3	Improve
		5	10		13		3	Improve
		6	15		15		0	No improve
		7	3		10		7	Improve
		10	4		8		4	Improve
		12	15		15		0	No improve
			Mean	S.D.	Mean	S.D.		
			8.56	4.82	10.33	4.72		
G4	pantomime of object use	1	43		38		−5	No improve
		2	37		26		−11	No improve
		3	39		43		4	Improve
		4	32		40		8	Improve
		5	31		24		−7	No improve
		6	41		45		4	Improve
		7	25		31		6	Improve
		10	23		25		2	Improve
		12	39		40		1	Improve
			Mean	S.D.	Mean	S.D.		
			34.44	7.09	34.67	8.22		
G5	actual tool use	1	19		19		0	No improve
		2	20		20		0	Ceiling
		3	20		20		0	Ceiling
		4	20		20		0	Ceiling
		5	20		20		0	Ceiling
		6	20		20		0	Ceiling
		7	19		20		1	Improve
		10	20		20		0	Ceiling
		12	20		20		0	Ceiling
			Mean	S.D.	Mean	S.D.		
			19.78	0.44	19.89	0.33		

executed within one practice block. During rest blocks, subjects were required to simply look at the red fixation cross which changed back to green after the rest interval, indicating the start of the next practice block.

Each patient completed 10 training sessions within 3 weeks time. Specifically, in week 1, there were four evening sessions, whereas weeks 2 and 3 had three evening sessions each.

2.5. Data analyses

All statistical analyses were performed with SPSS version 25 (www.ibm.com). Mean scores to the five Goldenberg test protocols were first tested for normality with the Shapiro-Wilk's test (both before and after the training) and then compared through paired sample *t*-tests. When no assumption of normal distribution of scores was met by one or more measures, the Wilcoxon signed-rank test for paired samples was performed.

Motor performance was measured in terms of speed and accuracy in

Fig. 1. The four-button key pad used in the MSLT. The task required participants to use 4 fingers of the left hand to complete an explicitly provided sequence of finger movements (4-1-3-2-4, where: 1 = index finger, 2 = middle finger, 3 = ring finger, 4 = little finger).

the execution of motor sequences. Mean duration (in seconds) of correct sequences and arcsin-transformed percentages of erroneous sequences were collected as dependent variables, with the help of *Presentation* software (NeuroBehavioral Systems, Berkely, USA; version 0.70), and submitted to two separate repeated-measures Analyses of Variance (ANOVA) with *Session* (one to ten) and *Block* (one to fourteen) as the within-participant variables. Furthermore, changes in duration of correct motor sequences were investigated within each session (i.e., between the first and the last block) and between the sessions (i.e., between the last block of session N-1 and the first block of session N) through two separate ANOVAs (see results section). These two analyses specifically probe within- and between-session performance improvements, respectively.

3. Results

Apraxia symptoms. Mean scores of Goldenberg test protocols G1 to G4, obtained *before* and *after* the MSLT training, followed a normal distribution. Scores from protocol G5, however, were not normally distributed before and after the MSLT training, due to ceiling effects (see Appendix-Table 1 for skewness and kurtosis values).

The mean scores of all 5 protocols numerically increased from the assessments performed *before* to after the 10 training sessions (see Table 2). However, only the increase in the score for the G3 protocol (*i.e.,* imitation of meaningless hand and finger gestures) was even considered marginally significant, $t(8) = 1.783$, $p = .056$ (one-tailed), whereas no significant differences were observed for G1 (imitation of meaningless hand postures), $t(8) = 1.305$, $p = .114$; G2 (imitation of meaningless finger postures), $t(8) = 1.098$, $p = .152$; G4 (pantomime of object use) $t(8) = 0.104$, $p = .460$; G5 (actual tool use), $Z = 1.000$, $p = .158$ (see Table 2).

Motor learning effects. A 10 (Session) x 14 (Block) ANOVA on the mean duration of correct sequences revealed a significant main effect of *Session*, $F(9, 72) = 26.430$, $p < .001$, $\eta^2_p = .77$. Follow-up, repeated contrasts of consecutive sessions showed that the duration of motor sequences decreased from session 1 to session 2, $F(1, 8) = 5.710$, $p = .044$, $\eta^2_p = .42$, from session 2 to session 3, $F(1, 8) = 25.673$, $p < .001$, $\eta^2_p = .76$, and then later from session 6 to session 7, $F(1, 8) = 8.126$, $p = .021$, $\eta^2_p = .50$; although the only change from session 2 to session 3 survived the Bonferroni-corrected $p = .006$. No further improvement was observed in later sessions, $Fs(1, 8) < 1.1$, $ps < .05$, $\eta^2_p s < .11$, reflecting the attainment of a performance plateau. This time-course was also specified by the polynomial contrast that was significant at quadratic level, $F(1, 8) = 44.350$, $p < .001$, $\eta^2_p = .85$ (Bonferroni-corrected $p = .025$). The main effect of *Block* was also significant, $F(13, 104) = 5.615$, $p < .001$, $\eta^2_p = .41$. Polynomial contrast revealed a significant linear fit, $F(1, 8) = 12.478$, $p = .008$, $\eta^2_p = .61$ (Bonferroni-corrected $p = .025$), as the duration of motor sequences decreased linearly from block 1 to block 14 (each block averaged performance across the 10 sessions). Last, the interaction between *Session* and *Block* was also significant, $F(117, 936) = 1.719$, $p < .001$, $\eta^2_p = .18$. Curve fitting analysis indicated that changes in movement speed across the 14 blocks over the course of the 10 sessions fit with a quadratic regression model, $F(1, 139) = 439.471$, $p < .001$; and improvements across blocks were greater in the early as compared to later sessions (Fig. 3a; see also Appendix-Fig. 2 for individual effects).

Analyses of the arcsin-transformed percentages of erroneous sequences (see Appendix-Fig. 1 for normality test) revealed a significant effect of *Session*, $F(9, 72) = 2.736$, $p = .008$, $\eta^2_p = .25$. Similar to the sequence duration results, a decreasing number of erroneous sequences was observed across the sessions. Specifically, polynomial contrast revealed a significant linear fit, $F(1, 8) = 9.391$, $p = .015$, $\eta^2_p = .54$ (Fig. 3b), indicating a linearly decreasing number of errors in performing sequences across sessions. No significant effects were observed for *Block*, $F(13, 104) = 0.746$, $p = .714$, $\eta^2_p = .08$ or *Session* × *Block* interaction, $F(117, 936) = 1.014$, $p = .446$, $\eta^2_p = .11$.

Within-sessions and between-sessions effects. Since the principal analysis revealed a decreasing duration of correct sequences across blocks and sessions, we conducted a follow-up analyses decomposing performance improvements into within- and between-session gains. Specifically, within-session improvements were computed as the difference between blocks 1 and 14 within the same session. A repeated-measures ANOVA was performed with *Session* (ten levels) as the within-participants variable, which was significant, $F(9, 72) = 2.591$, $p = .012$, $\eta^2_p = .24$. Differences were all positive and decreased linearly across the sessions, as indicated by significant polynomial contrasts at linear level, $F(1, 8) = 9.697$, $p = .014$, $\eta^2_p = .55$ (Fig. 4a). Between-session improvements were computed as the difference between block 14 of session N and block 1 of session N+1. A repeated-measures ANOVA was performed with *Between-sessions difference* (nine levels) as the within-participant variable, which was not significant, $F(8, 64) = 0.669$, $p = .717$, $\eta^2_p = .08$. Differences were mostly negative, with no significant trend across sessions (Fig. 4b). Results clarified that the general improvements in movement speed revealed in the principal analysis were due to within-session, but not between-session, gains.

4. Discussion

Ideomotor apraxia is characterized by a loss of higher motor functions, like imitation and pantomime despite the preserved basic motor and sensory functions. The motivation for this study was to examine if

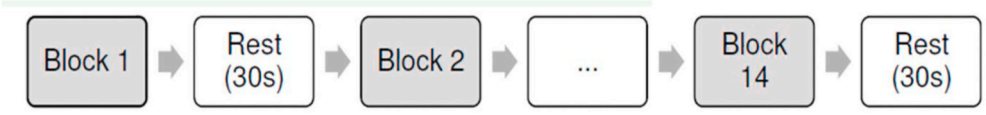

Fig. 2. Design of a single training session where blocks of rest were interspersed with blocks of active task practice. Each block consisted of 30 key presses, ideally corresponding to 6 correct repetitions of the 5-element sequence.

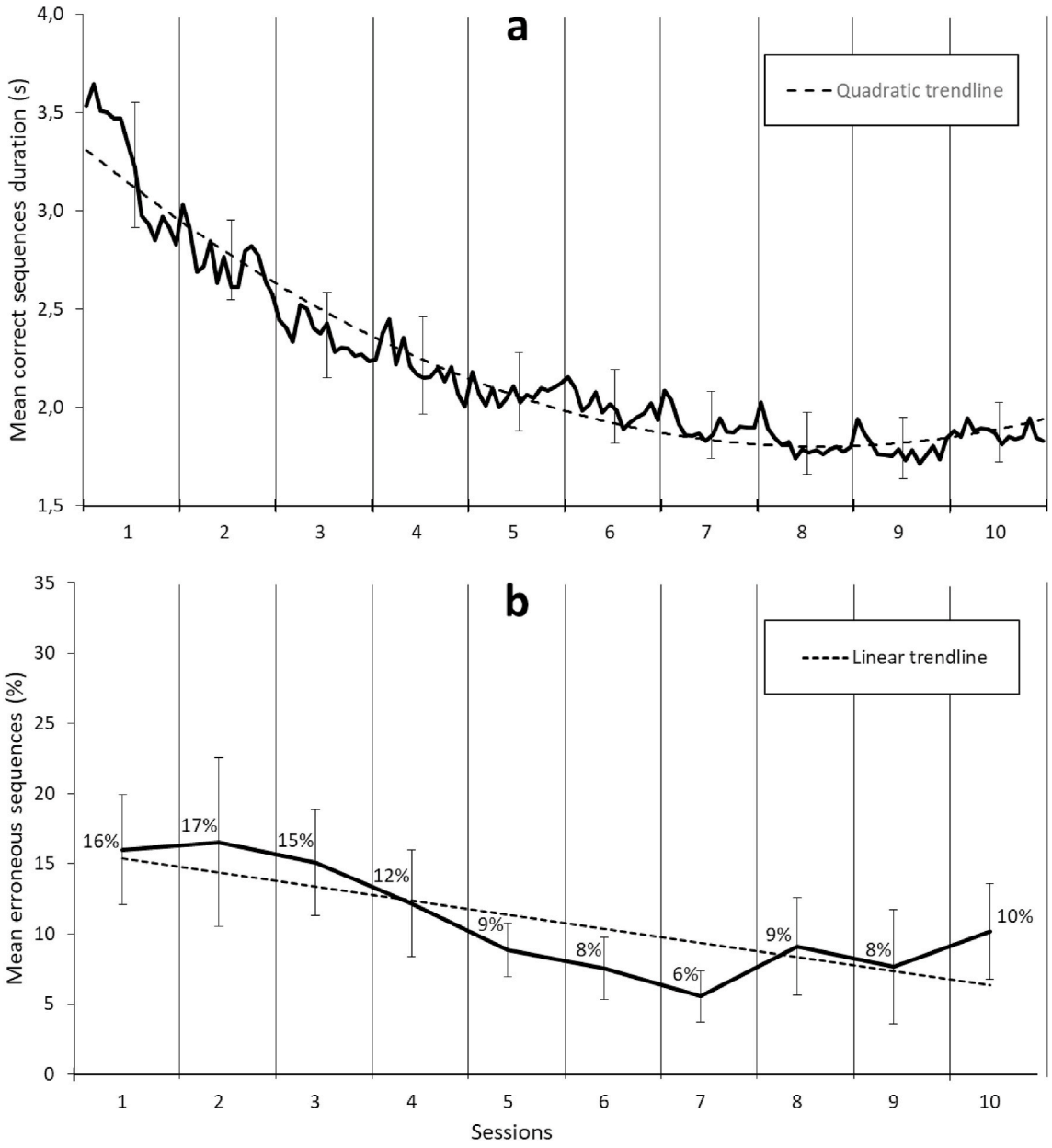

Fig. 3. The effect functions display: a) a decreasing pattern of correct sequence durations across blocks over the course of the sessions, and b) a decreasing pattern for percentages of erroneous sequences across the sessions. Significantly fitting quadratic and linear trend lines are represented in panels (a) and (b), respectively. Standard error bars for levels of session are reported.

these patients with a loss of motor functioning can still learn new explicit motor skills. Therefore, the present pilot study investigated, by means of an explicit MSLT paradigm, the acquisition and retention of novel motor sequences across ten sessions over three weeks of task performance in a group of patients with ideomotor apraxia. To our knowledge, this represents the first attempt to study explicit motor learning in patients with ideomotor apraxia by application of an extensively studied MSLT.

Our findings demonstrate that speed and accuracy of motor sequence performance improved across training sessions carried out in the evening. This was consistent with findings of a recent and similar investigation in elderly (Gal et al., 2019) and is consistent with the view that evening training is a suitable time for motor skill learning (especially in older adults). More specifically, performance improvement (i.e. duration of motor sequences) across training blocks was more pronounced in early as compared to later sessions. This suggests that extensive motor training may not need to last for longer periods to maximize motor learning effects. Improvement was less reliable for accuracy, a result that was not surprising since accuracy has often demonstrated to be less modulated by learning/practice (King et al., 2017; Gal et al., 2019). Additionally, our data suggest some weak evidence for a positive effect of MSLT training on the imitation of hand and finger gestures.

There is existing evidence that patients with limb apraxia can show implicit motor learning in a SRTT (Serial Reaction Time Task) (Dovern et al., 2011). Specifically, it was demonstrated that despite showing overall slower RTs, apraxic patients displayed an amount of sequence-specific motor learning that was comparable to that of non-apraxic patients and healthy controls. However, apraxic patients showed reduced intentional retrieval of the learned sequence. Dovern et al. (2011) concluded that incidental motor learning could be of benefit for apraxia treatment, but that automatic rather than intentional retrieval strategies should be enforced.

Most important, in our study, we found that patients with ideomotor

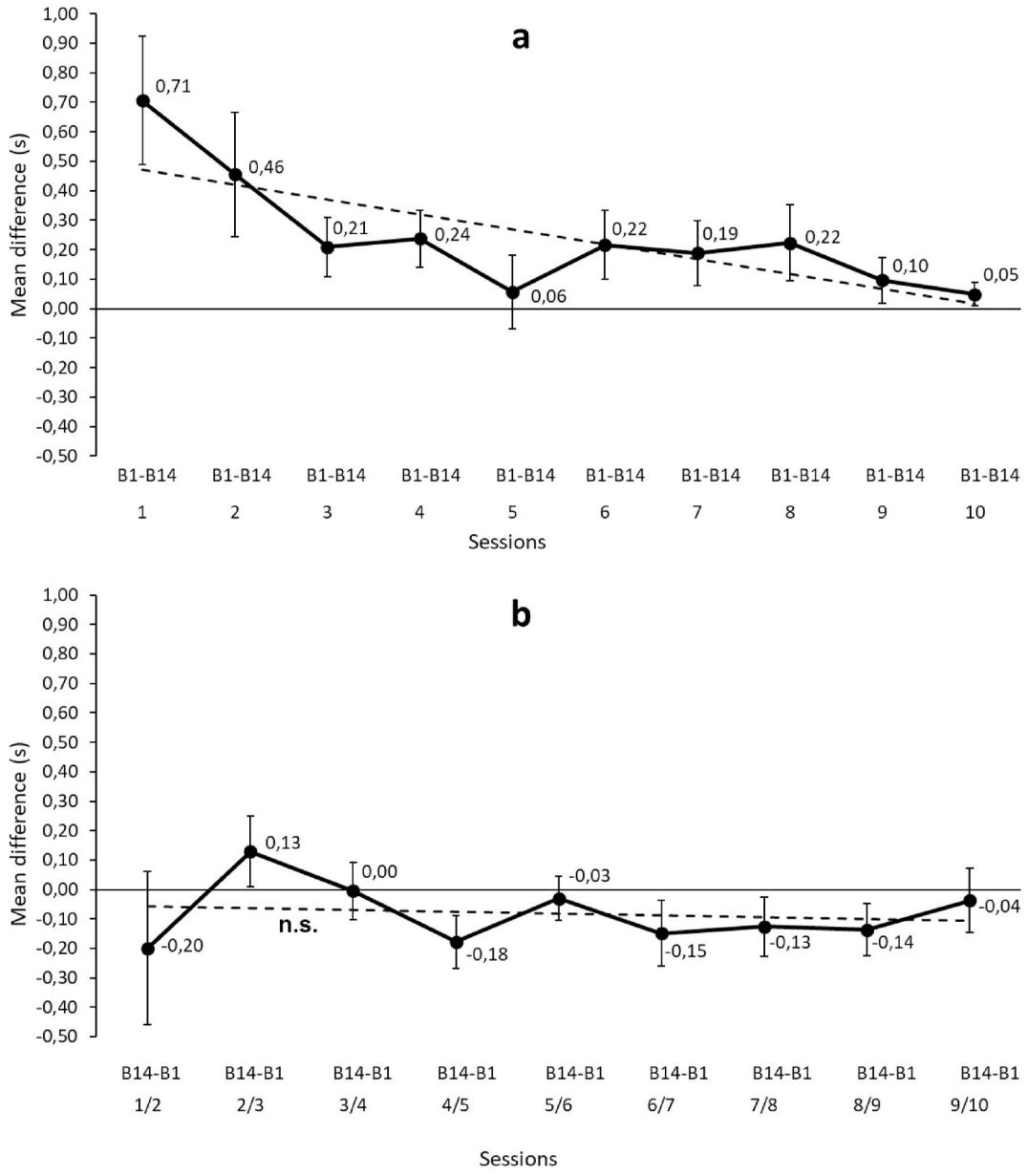

Fig. 4. a) Difference between blocks 1 and 14 with each session, reflecting within-session gains in performance. Linear trend line illustrates a significantly decreasing effect function. b) Difference between block 14 of session N and block 1 of session N+1, reflecting between-session gains in performance. Linear trend line refers to nonsignificant effect function. Standard error bars for blocks are reported.

apraxia were able to learn a new motor sequence across three weeks of training. Since the patients performed the training with the left, ipsilesional hand, they could use the motor networks of the right hemisphere. On the other hand, at least in right-handed individuals, the higher motor plans and concepts are generally attributed to the left hemisphere (Janssen et al., 2011) and thus it is possible that our patients may have relied on the non-affected structures of the left side.

The question arises about which neural mechanisms remain less affected in our apraxia patients, which allowed for a significant learning of motor sequences despite impaired imitation and pantomime. There are many functional neuroimaging studies that addressed the neural correlates of motor sequence learning in healthy young participants (Buxbaum et al., 2008; Debas et al., 2010; Doyon et al., 2009; Doyon and Benali, 2005; Karni, 1995, 1996, 1996; King et al., 2013; Lehéricy et al., 2005; Ungerleider et al., 2002). During MSL, widespread activation in the cortico-cerebellar, cortico-striatal and cortico-hippocamppal networks are described by King et al. (2013, 2017) and Debas et al. (2014). In the initial phase of motor sequence learning, motor areas, that is premotor cortex (PM), primary motor cortex (M1), supplementary motor area (SMA), and prefrontal cortex (PFC), as well as the superior parietal lobule (SPL), the basal ganglia (especially striatum, putamen), the hippocampus, the thalamus, and the cerebellum are activated. In later learning phases, activation in the cerebellum is known to decrease while activation in the striatum increases (Debas et al., 2014; Seitz, 2001). Debas et al. (2014) describe a greater activity and integration within the cortico-striatal network in the off-line consolidation phase. There is evidence that especially the cortico-striatal network and the hippocampus are important for long-term retention and consolidation of memory traces (Albouy et al., 2013; King et al., 2017). A very recent study highlighted again the role of dorsal premotor and superior parietal cortices in short term motor sequence learning (Yokoi and Diedrichsen, 2019) which occurs at the interface of cognitive and motor systems but is largely driven by cognitive processes (Ariani and Diedrichsen, 2019). Hardwick et al. (2015) studied the resting state connectivity of the

dorsal premotor cortex as a hub for motor learning using different meta-analytical connectivity methods on very large number of samples. They found a robust connectivity spanning prefrontal, premotor, and parietal regions and argue that dPMC acts as an interface between motor control and cognition.

We did not perform a systematic lesion analysis, and therefore we can only remain descriptive at this point. From the patients' records, all stroke lesions were localized in the territory of the left middle cerebral artery, therefore containing lesions of the inferior parietal and inferior frontal lobes. This fits the idea that ideomotor apraxia results from lesions of brain areas of the ventro-dorsal stream containing the inferior parietal and inferior premotor areas (Binkofski and Fink, 2005; Pisella et al., 2006; Binkofski and Buxbaum, 2013; Binkofski, 2020). These areas on the left side are crucial for processing of planning and conception of actions. But, areas of the dorso-dorsal stream which are responsible for more online processing of motor acts remained unaffected. Dorsal premotor and superior parietal areas identified by Yokoi and Diedrichsen (2019) and Hardwick et al. (2015) belong to the dorso-dorsal stream. Therefore, it may follow that the online planning in motor sequence learning (Ariani and Diedrichsen, 2019) is processed also in the dorso-dorsal stream. On the other hand, brain structures like cerebellum, striatum and hippocampus, which are important in the early phase of acquisition, in the consolidation and retention were not affected by stroke.

In our patients group, higher motor functions, like imitation and pantomime, were impaired due to affected crucial structures of the left hemisphere. Whether motor learning is also possible in patients with the most profound apraxic deficit, namely the impairment of object use, still remains to be investigated in future studies.

As far as the symptoms of apraxia are concerned, we can make only weak inferences about possible carry-over effects from MSLT training on the clinical symptoms of our patients. According to Ariani and Diedrichsen (2019), MSLT contains elements of motor planning; therefore, it is theoretically possible that such carry over effects can happen. The weak significant improvement in the apraxia scores can, for example, originate in the small number of patients in our pilot study. But, it is worth explicitly stating that we observed only a trend for a significant effect in one of the 5 Goldenberg protocols, and the effects of the training program on apraxia symptoms can be considered weak at best. Nonetheless, it is important to remark that patients with ideomotor apraxia are able to explicitly learn motor skills. This knowledge may inform the design of future treatment schemas which should contain many repetitions of the same action.

4.1. Limitations

The present study was based on a rather small number of accessible patients. The major reason is that it has been hard to motivate patients with apraxia to complete three weeks of training; this resulted, even in our small sample, in three drop outs because of incomplete data. To possibly improve the adherence of the patients, our findings suggest that shorter training periods could be applied. Nevertheless, we believe that the results of this pilot study suggest that apraxic patients, with disturbance of imitation and pantomime (ideomotor apraxia), can learn explicit motor sequences in a long term training protocol. Logically, the next step should be to extend the study to patients with ideatory apraxia.

A second limitation is the absence of a control group. On the one hand, we can argue that a control group may not be overly informative, as we would expect their baseline motor execution (i.e., performance on the first blocks) to be much better than patients and thus not on the same scale (thus making any comparisons between healthy older and stroke patients difficult). To cope with this limitation, we discussed our results in the light of Gal et al. (2019) which employed identical study design applied to healthy participants. Our patients were slower in execution than healthy participants, but showed a motor learning path that was comparable to them.

Third, our design does not allow us to definitively conclude that the observed performance improvements were in fact specific to the acquired motor sequence as opposed to more general, non-sequence-specific improvements in task performance. It is worth noting that previous research employing similar tasks and designs have demonstrated sequence-specific learning across the lifespan (Dorfberger et al., 2012; Robertson et al., 2004; Brown et al., 2009; Gann et al., 2021 in press) so it is likely that the improvements observed in apractic patients in the current study also reflect sequence-specificity. This, however, was not explicitly tested and thus warrants further investigation in future research. It is also worth noting that even though the task is considered an explicit learning paradigm, we cannot discount the contributions of possible, concurrent implicit learning processes.

Finally, as far as the issue of the transfer from MSLT to the improvement of the apraxia symptoms is concerned, the mild effects we observed are of low effect size and it is unclear whether similar effects would be replicated in a larger population of patients.

Authors contribution statement

SW – performed all neuropsychological testing, most of the MSLT testing and wrote the first draft of the paper, MA – recruited most of the patients, performed part of the MSLT testing and participated on the data analysis, AK – contributed significantly to the concept of the study and helped in the data analysis, CG – worked on the concept for the study and participated in the data analysis, JD – created the theoretical framework of the study, BRK – provided significant input to the data analysis and worked significantly on the text, JC – supervised the data collection and the writing of the paper, JJR – provided significantly to the data analysis and the interpretation of the data, GB – provided the theoretical background of the paper, AP – performed most of the data analysis and worked significantly on the paper revision, JK – supervised most of the study, FB – supervised the concept of the study, provided most of the clinical aspects of the study, supervised the data collection, the data analysis and the writing.

Acknowledgments

The study was funded by the German Ministry for Education and Research (BMBF), ERANET-NEURON, project COGSTROKE (01EW1203).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2021.107921.

References

Albouy, G., King, B., Marquet, P., Doyon, J., 2013. Hippocampus and striatum: dynamics and interaction during acquisition and sleep-related motor sequence memory consolidation. Hippocampus 23 (11), 985–1004. https://doi.org/10.1002/hipo.22183.

Ant, J.M., Niessen, E., Achilles, E.I.S., Saliger, J., Karbe, H., Weiss, P.H., Fink, G.R., 2019. Anodal tDCS over left parietal cortex expedites recovery from stroke-induced apraxic imitation deficits: a pilot study. Neurological Research and Practice. https://doi.org/10.1186/s42466-019-0042-0.

Ariani, G., Diedrichsen, J., 2019. Sequence learning is driven by improvements in motor planning. J. Neurophysiol. 121 (6), 2088–2100. https://doi.org/10.1152/jn.00041.2019.

Binkofski, F., Fink, G.R., 2005. Apraxias. Nervenarzt 76, 493–511. https://doi.org/10.1007/s00115-005-1908-7.

Binkofski, F., Buxbaum, L.J., 2013. Two action systems in the human brain. Brain Lang. 127 (2), 222–229.

Binkofski, F., 2020. Apraxien. Neurologie up2date 3, 275–294. https://doi.org/10.1055/a-0943-0986, 03.

Binkofski, F., Klann, J., 2013. Die Apraxie der oberen Gliedmaßen. Fachzeitschrift NOT 5, 24–26.

Brown, R.M., Robertson, E.M., Press, D.Z., 2009. Sequence skill acquisition and off-line learning in normal aging. PloS One 4 (8), e6683. https://doi.org/10.1371/journal.pone.0006683.

Buxbaum, L.J., Haaland, K.Y., Hallett, M., Wheaton, L., Heilman, K.M., Rodriguez, A., Rothi, L.J.G., 2008. Treatment of limb apraxia: moving forward to improved action. Am. J. Phys. Med. Rehab. https://doi.org/10.1097/PHM.0b013e31815e6727.

Buxbaum, L.J., Randerath, J., Vallar, G., 2018. Chapter 17 - limb apraxia and the left parietal lobe. In: H B B T-H of C, Coslett, N. (Eds.), The Parietal Lobe, vol. 151. Elsevier, pp. 349–363. https://doi.org/10.1016/B978-0-444-63622-5.00017-6.

Censor, N., Sagi, D., Cohen, L.G., 2012. Common mechanisms of human perceptual and motor learning. Nat. Rev. Neurosci. https://doi.org/10.1038/nrn3315.

Dahms, C., Brodehl, S., Witte, O.W., Klingers, C.M., 2019. The importance of diferent learning stages for motor sequence learning afer stroke. Hum. Brain Mapp. 41 (1), 270–286. https://doi.org/10.1002/hbm.24793.

Debas, K., Carrier, J., Barakat, M., Marrelec, G., Bellec, P., Tahar, A.H., Doyon, J., 2014. Off-line consolidation of motor sequence learning results in greater integration within a cortico-striatal functional network. Neuroimage. https://doi.org/10.1016/j.neuroimage.2014.05.022.

Debas, K., Carrier, J., Orban, P., Barakat, M., Lungu, O., Vandewalle, G., Doyon, J., 2010. Brain plasticity related to the consolidation of motor sequence learning and motor adaptation. In: Proceedings of the National Academy of Sciences of the United States of America. https://doi.org/10.1073/pnas.1013176107.

Dorfberger, S., Adi-Japha, E., Karni, A., 2012. Sequence specific motor performance gains after memory consolidation in children and adolescents. PloS One 7 (1), e28673. https://doi.org/10.1371/journal.pone.0028673.

Dovern, A., Fink, G.R., Weiss, P.H., 2011. How to diagnose and treat limb apraxia. Fortschritte Der Neurologie Psychiatrie. https://doi.org/10.1055/s-0029-1246097.

Doyon, J., Gabitov, E., Vahdat, S., Lungu, O., Boutin, A., 2018. Current issues related to motor sequence learning in humans. Curr. Opin. Behav. Sci. 20, 89–97. https://doi.org/10.1016/j.cobeha.2017.11.012.

Doyon, Julien, Benali, H., 2005. Reorganization and plasticity in the adult brain during learning of motor skills. Curr. Opin. Neurobiol. https://doi.org/10.1016/j.conb.2005.03.004.

Doyon, J., Korman, M., Morin, A., Dostie, V., Tahar, A.H., Benali, H., Carrier, J., 2009. Contribution of night and day sleep vs. simple passage of time to the consolidation of motor sequence and visuomotor adaptation learning. Exp. Brain Res. https://doi.org/10.1007/s00221-009-1748-y.

Fullerton, K.J., Mcsherry, D., Stout, R.W., 1986. Albert's test: a neglected test of Perceptual neglect. Lancet. https://doi.org/10.1016/S0140-6736(86)92381-0.

Gal, C., Gabitov, E., Maaravi-Hesseg, R., Karni, A., Korman, M., 2019. A delayed advantage: multi-session training at evening hours leads to better long-term retention of motor skill in the elderly. Front. Aging Neurosci. 11, 321. https://doi.org/10.3389/fnagi.2019.00321.

Gann, M.A., King, B.R., Dolfen, N., Veldman, M.P., Chan, K.L., Puts, N.A.J., Edden, R.A.E., Davare, M., Swinnen, S.P., Mantini, D., Robertson, E.M., Albouy, G., 2021. Hippocampal and striatal responses during motor learning are modulated by prefrontal cortex stimulation, 118158 Neuroimage 12, 237. https://doi.org/10.1016/j.neuroimage.2021.118158. Epub ahead of print. PMID: 33991699.

Goldenberg, G., Spatt, J., 2009. The neural basis of tool use. Brain. https://doi.org/10.1093/brain/awp080.

Goldenberg, G., 1996. Defective imitation of gestures in patients with damage in the left or right hemispheres. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp.61.2.176.

Goldenberg, G., 2009. Apraxia and the parietal lobes. Neuropsychologia 47 (6), 1449–1459.

Goldenberg, Georg, 2013. Apraxia. Wiley Interdisciplinary Reviews: Cognitive Science. https://doi.org/10.1002/wcs.1241.

Goldenberg, Georg, 2015. Apraxia. International Encyclopedia of the Social & Behavioral Sciences, second ed. https://doi.org/10.1016/B978-0-08-097086-8.56002-4

Goldenberg, Georg, Hermsdörfer, J., Glindemann, R., Rorden, C., Karnath, H.O., 2007. Pantomime of tool use depends on integrity of left inferior frontal cortex. Cerebr. Cortex. https://doi.org/10.1093/cercor/bhm004.

Goldenberg, Georg, Karnath, H.O., 2006. The neural basis of imitation is body part specific. J. Neurosci.: Off. J. Soc. Neurosci. https://doi.org/10.1523/JNEUROSCI.0638-06.2006.

Hardwick, R.M., Lasage, E., Eickhoff, C.R., Clos, M., Fox, P., Eickhoff, S.B., 2015. Multimodal connectivity of motor learning-related dorsal premotor cortex. Neuroimage 123, 114–128.

Hautzinger, M., Keller, F., Kühner, C., 2006. Beck depressions-inventar (BDI-II). Revision. Resport Psychol. https://doi.org/10.1097/AAP.0000000000000142.

Heilman, K.M., Schwartz, H.D., Geschwind, N., 1975. Defective motor learning in ideomotor apraxia. Neurology. https://doi.org/10.1212/wnl.25.11.1018.

Janssen, L., Meulenbroek, R.G.J., Steenbergen, B., 2011. Behavioral evidence for left-hemisphere specialization of motor planning. Exp. Brain Res. 209, 65–72. https://doi.org/10.1007/s00221-010-2519-5.

Karni, A., 1995. When practice makes perfect. Lancet. https://doi.org/10.1016/S0140-6736(95)90386-0.

Karni, A., 1996. The acquisition of perceptual and motor skills: a memory system in the adult human cortex. Cognitive Brain Research. https://doi.org/10.1016/S0926-6410(96)00039-0.

Karni, A., Meyer, G., Jezzard, P., Adams, M.M., Turnert, R., Ungerleider, L.G., 1995. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. Nature 377 (6545), 155–158. https://doi.org/10.1038/377155a0.

King, B.R., Rumpf, J.J., Heise, K.F., Veldman, M.P., Peeters, R., Doyon, J., Classen, J., Albouy, G., Swinnen, S.P., 2020a. Lateralized effects of post-learning transcranial direct current stimulation on motor memory consolidation in older adults: an fMRI investigation. Neuroimage 223, 117323. https://doi.org/10.1016/j.neuroimage.2020.117323.

King, B.R., Rumpf, J.J., Verbaanderd, E., Heise, K.F., Dolfen, N., Sunaert, S., Doyon, J., Classen, J., Mantini, D., Puts, N.A.J., Edden, R.A.E., Albouy, G., Swinnen, S.P., 2020b. Baseline sensorimotor GABA levels shape neuroplastic processes induced by motor learning in older adults. Hum. Brain Mapp. 41 (13), 3680–3695. https://doi.org/10.1002/hbm.25041.

King, B.R., Fogel, S.M., Albouy, G., Doyon, J., 2013. Neural correlates of the age-related changes in motor sequence learning and motor adaptation in older adults. Frontiers in Human Neuroscience. https://doi.org/10.3389/fnhum.2013.00142.

King, B.R., Saucier, P., Albouy, G., Fogel, S.M., Rumpf, J.J., Klann, J., et al., 2017. Cerebral activation during initial motor learning forecasts subsequent sleep-facilitated memory consolidation in older adults. Cerebr. Cortex. https://doi.org/10.1093/cercor/bhv347.

King, B.R., Hoedlmoser, K., Hirschauer, F., Dolfen, N., Albuoy, G., 2017. Sleeping on the motor engram: the multifaceted nature of sleep-related motor memory consolidation. Neurosci. Biobehav. Rev. 8, 1–22.

Korman, M., Doyon, J., Doljansky, J., Carrier, J., Dagan, Y., Karni, A., 2007. Daytime sleep condenses the time course of motor memory consolidation. Nat. Neurosci. https://doi.org/10.1038/nn1959.

Krakauer, J.W., Shadmehr, R., 2006. Consolidation of motor memory. Trends in Neurosciences. https://doi.org/10.1016/j.tins.2005.10.003.

Lehéricy, S., Benali, H., Van De Moortele, P.F., Pélégrini-Issac, M., Waechter, T., Ugurbil, K., Doyon, J., 2005. Distinct basal ganglia territories are engaged in early and advanced motor sequence learning. In: Proceedings of the National Academy of Sciences of the United States of America. https://doi.org/10.1073/pnas.0502762102.

Laventure, S., Pinsard, B., Lungu, O., Carrier, J., Fogel, S., Benali, H., Lina, J.-M., Boutin, A., Doyon, J., 2018. Beyond spindles: interactions between sleep spindles and boundary frequencies during cued reactivation of motor memory representations. Sleep 41 (9), zsy142. https://doi.org/10.1093/sleep/zsy142.

Margraf, J, Ehlers, A., 2007. Das Beck-Angstinventar (BAI). Springer.

Mengotti, P., Corradi-Dell'Acqua, C., Negri, G.A.L., Ukmar, M., Pesavento, V., Rumiati, R.I., 2013. Selective imitation impairments differentially interact with language processing. Brain. https://doi.org/10.1093/brain/awt194.

Motomura, N., Seo, T., Asaba, H., Sakai, T., 1989. Motor learning in ideomotor apraxia. Int. J. Neurosci. https://doi.org/10.3109/00207458908987424.

Mühlau, M., Hermsdörfer, J., Goldenberg, G., Wohlschläger, A.M., Castrop, F., Stahl, R., Röttinger, M., Erhard, P., Haslinger, B., Ceballos-Baumann, A.O., Conrad, B., Boecker, H., 2005. Left inferior parietal dominance in gesture imitation: an fMRI study. Neuropsychologia 43 (7), 1086–1098. https://doi.org/10.1016/j.neuropsychologia.2004.10.004. Epub 2005 Jan 5.

Niessen, E., Fink, G.R., Weiss, P.H., 2014. Apraxia, pantomime and the parietal cortex. Neuroimage: Clinical. https://doi.org/10.1016/j.nicl.2014.05.017.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. https://doi.org/10.1016/0028-3932(71)90067-4.

Pérez-Mármol, J.M., García-Ríos, M.C., Barrero-Hernandez, F.J., Molina-Torres, G., Brown, T., Aguilar-Ferrándiz, M.E., 2015. Functional rehabilitation of upper limb apraxia in poststroke patients: study protocol for a randomized controlled trial. Trials 16 (1), 508. https://doi.org/10.1186/s13063-015-1034-1.

Pisella, L., Binkofski, F., Lasek, K., Toni, I., Rossetti, Y., 2006. No double-dissociation between optic ataxia and visual agnosia: multiple sub-streams for multiple visuo-manual integrations. Neuropsychologia 44 (13), 2734–2748.

Robertson, E.M., Pascual-Leone, A., Press, D.Z., 2004. Awareness modifies the skill-learning benefits of sleep. Curr. Biol. 14, 208–212. https://doi.org/10.1016/j.cub.2004.01.027.

Rothi, L.J.G., Heilman, K.M., 1984. Acquisition and retention of gestures by apraxic patients. Brain Cognit. https://doi.org/10.1016/0278-2626(84)90032-0.

Rumiati, R.I., Papeo, L., Corradi-Dell'Acqua, C., 2010. Higher-level motor processes. Ann. N. Y. Acad. Sci. https://doi.org/10.1111/j.1749-6632.2010.05442.

Rumpf, J.J., Wegscheider, M., Hinselmann, K., et al., 2017. Enhancement of motor consolidation by post-training transcranial direct current stimulation in older people. Neurobiol. Aging 49, 1–8. https://doi.org/10.1016/j.neurobiolaging.2016.09.003.

Seitz, R.J., 2001. Motorisches Lernen: untersuchungen mit der funktionellen Bildgebung. Deutsche Zeitschrift für Sportmedizin 52 (12), 343–349.

Ungerleider, L.G., Doyon, J., Karni, A., 2002. Imaging brain plasticity during motor skill learning. Neurobiology of Learning and Memory. https://doi.org/10.1006/nlme.2002.4091.

Walker, M.P., Brakefield, T., Hobson, J.A., Stickgold, R., 2003. Dissociable stages of human memory consolidation and reconsolidation. Nature. https://doi.org/10.1038/nature01930.

Weiss, C., Tsakiris, M., Haggard, P., Schütz-Bosbach, S., 2014. Agency in the sensorimotor system and its relation to explicit action awareness. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2013.09.034.

Yokoi, A., Diedrichsen, J., 2019. Neural organization of hierarchical motor sequence representations in the human neocortex. Neuron 103 (6), 1178–1190. https://doi.org/10.1016/J.NEURON.2019.06.017 e7.