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Implicit learning of perceptual sequences is preserved in Parkinson's disease

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ABSTRACT

Background: Various studies investigated implicit sequence learning in Parkinson's disease (PD) by means of the traditional motor Serial Reaction Time (SRT) task and found a general pattern of impaired sequence learning. However, as perceptual and motor sequences of the SRT-task were correlated in previous studies, implicit sequential knowledge acquisition that is tested independently from motor sequences remains to be determined in PD.

Objective: In this study, we investigated implicit sequence learning independently from motor sequence learning in individuals with PD. To this end, we used a perceptual SRT-task that did not rely upon sequential motor knowledge.

Methods: We measured response times (RTs) of 19 participants with PD (Hoehn & Yahr II or III; mean age 65) and 18 age-matched healthy controls (HC) (mean age 61.5) in a perceptual SRT-task. General learning effects and sequence-specific learning effects were analyzed using repeated measures ANOVAs.

Results: A significant decreasing linear trend ($p < .001$) in RTs was revealed in both the PD and HC groups as the SRT-task progressed, indicating general learning effects. Notably, a significant, strong main effect of sequence-specific learning occurred ($p < .001$), irrespective of group ($p = .436$). Sequence-specific learning did not differ significantly between the PD ($M = 156.5$ ms; $SD = 50.7$) and HC group ($M = 173.0$ ms; $SD = 104.2$). Bayesian analyses confirmed this as evidence of absence of an effect ($B_{01} = 3.543$).

Conclusions: Our results suggest that, at least in Hoehn & Yahr stages II and III, implicit sequential knowledge acquisition may be preserved in individuals with PD, when tested independently from motor sequence learning.

Keywords: Parkinson's Disease, Procedural Learning, Serial Reaction Time Task, Implicit Sequence Learning, Perceptual Sequence Learning

KEY POINTS

- Question: Is implicit sequence learning preserved in PD, when investigated independently from motor sequence learning?
- Findings: We found preserved implicit knowledge acquisition of perceptual sequences in individuals with PD.
- Importance: These findings provide more insight in the underlying cognitive processes that are affected in sequential skill learning in PD.
- Next Steps: Investigating to what extent these findings can be generalized to the PD population, considering cognitive status, disease status, medication status.

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1. INTRODUCTION

Parkinson's disease (PD) is the most common movement disorder and represents the second most common neurodegenerative disease after Alzheimer's disease (Lebouvier et al., 2009). Occurring in about 1% of people over the age of 65, it is considered the fastest growing neurological disorder in the world (Siegert et al., 2006). As the average age of the world's population increases steadily, the number of people with PD has doubled to over 6 million in the past 3 decades and is projected to double again to over 12 million by 2040 (Dorsey et al., 2018).

PD is caused by the degeneration of dopamine-producing cells in the basal ganglia (Dauer & Przedborski, 2003; Dickson, 2018; Fearnley & Lees, 1991). Reduced dopamine levels in the basal ganglia give rise to a cascade of activity changes in the basal ganglia-thalamocortical circuit and interconnected areas, including the cerebellum and the pedunculopontine nucleus (Horiba et al., 2019; Simpson & Mak, 2019; Tao Wu et al., 2012). Dopamine depletion leads to the typical major motor signs of the disease, such as tremor, rigidity, bradykinesia and postural instability (Horiba et al., 2019; Jankovic, 2008; Lang & Lozano, 1998; Mathys et al., 2016; Simpson & Mak, 2019; T Wu et al., 2010) – but also to cognitive impairment (attention, executive functions, memory, learning) (Aarsland et al., 2010; Giordano et al., 2017) and neurobehavioral abnormalities (loss of interest, anxiety, depression) (Jankovic, 2008).

Because of the prominent motor complaints and symptoms, PD was initially labelled a movement disorder. In recent years, however, it has been increasingly recognized that cognitive impairment and neurobehavioral abnormalities, such as dementia, depression, psychosis and impulse control disturbance appear to be widespread among individuals with PD (Draijer et al., 2011; Jankovic, 2008; Pagonabarraga & Kulisevsky, 2012). Cognitive deficits can be present from the earliest stages (Pagonabarraga & Kulisevsky, 2012), even when subtle changes are not yet apparent to the patient or clinician (Foltynie et al., 2004; Mamikonyan et al., 2009; Muslimović et al., 2005; Pagonabarraga & Kulisevsky, 2012). Cognitive impairment in the absence of frank dementia, typically called mild

cognitive impairment (MCI), is estimated to occur in 18 to 36% of individuals newly diagnosed with PD (Aarsland et al., 2009; Foltynie et al., 2004; Janvin et al., 2003; Williams-Gray et al., 2007).

One particular form of cognitive function that has been studied extensively in PD is implicit sequence learning. Implicit sequence learning is a type of procedural learning that is defined as the ability to acquire sequential skill without intention and without the need for conscious awareness (Deroost et al., 2018; Hashemirad et al., 2016; Ruitenberg et al., 2015; Siegert et al., 2006). The “implicit” aspect of learning refers to the observation that an individual’s performance on a particular task reflects learning that greatly exceeds the ability to provide an informative, verbal account of the acquired skill (Siegert et al., 2006). Neostriatal structures such as the basal ganglia play a key role in implicit sequence learning abilities (Deroost et al., 2006; Hayes et al., 2015; Stephan et al., 2011; Vandenbossche et al., 2013; Wilkinson et al., 2009). For this reason, implicit sequence learning in PD – a prime model of basal ganglia dysfunction – has received substantial interest (Deroost et al., 2006; Dominey et al., 1997; Ferraro et al., 1993; Gamble et al., 2014; Hayes et al., 2015; Jackson et al., 1995; Ruitenberg et al., 2015; Siegert et al., 2006; J. Smith et al., 2001; J. G. Smith & McDowall, 2004; Stephan et al., 2011; Vandenbossche et al., 2009, 2013; Wilkinson et al., 2009).

Implicit sequence learning is predominantly investigated by means of the Serial Reaction Time (SRT) task, originally introduced in 1987 (Nissen & Bullemer, 1987). Its popularity is due to its easy implementation, both in healthy and clinical populations, and its capacity to capture sequential learning on-line, i.e. during execution of the task. In a typical SRT-task, a visual stimulus (e.g. black dot) is presented in one of four horizontal locations on a computer screen. Participants are asked to react to the target location as fast as possible by pressing a spatially compatible response key (Savic & Meier, 2016). Participants are not informed that the order of target locations follows a sequence predetermined by the experimenter (Deroost et al., 2018; Savic & Meier, 2016). Participants are trained on the sequence for several blocks of trials. Typically, response times (RTs) decrease progressively with practice. This is referred to as a general learning effect. It provides general performance-related information (e.g. general motor performance, effects of task routine) and is also

regarded as a preliminary indication for sequence learning (Deroost et al., 2018). Crucially, RTs increase when the sequence is inconspicuously replaced by a random sequence and decrease again when the predetermined sequence is reintroduced. The latter is referred to as the sequence-specific learning effect and is calculated by subtracting the mean RTs of the adjacent sequenced blocks from the RTs in the random block.

Using the SRT-task, the majority of previous studies¹ showed that implicit sequence learning is impaired in PD (Deroost et al., 2006; Ferraro et al., 1993; Gamble et al., 2014; Jackson et al., 1995; Stephan et al., 2011; Vandenbossche et al., 2009, 2013; Wilkinson et al., 2009), although others have observed small or no impairments compared to a healthy control group (Gobel et al., 2013; Kelly et al., 2004; Seidler et al., 2007; J. Smith et al., 2001; Werheid et al., 2003). Recent meta-analyses, however, confirm a general pattern of disrupted sequential knowledge acquisition in this population (Clark et al., 2014; Hayes et al., 2015; Siegert et al., 2006).

An important issue in traditional SRT-task research is that the motor demands of the task may prevent the expression of any acquired sequential knowledge in individuals with PD (Packard & Knowlton, 2002). A number of studies have attempted to circumvent this problem by reducing the motor component of the SRT-task to investigate whether the 'underlying' sequential skill is still intact. For instance, some studies employed a verbal version of the classic SRT-task, in which the classic manual response was replaced by an oral response (J. Smith et al., 2001; J. G. Smith & McDowall, 2004; Westwater et al., 1998). Participants in these studies had to verbally indicate the location of the visual stimulus as soon as possible, by saying aloud the number corresponding to its location (i.e. "one", "two", "three" or "four"). Using this verbal SRT-task, Smith et al. (2001) demonstrated preserved implicit sequence learning in participants with PD and age-matched healthy controls (J. Smith et al., 2001). However, two studies implementing the same verbal SRT-task still found significantly impaired

¹ Although some studies referenced here define 'learning' as a relatively permanent change in performance that's measured after a period of no practice (Edwards, 2010; Soderstrom & Bjork, 2015), i.e., based on a retention test (Vakil et al. 2000; Werheid et al. 2003), most investigated acquisition of sequential knowledge (Deroost et al., 2006; Ferraro et al., 1993; Jackson et al., 1995; Kelly et al., 2004; J. Smith et al., 2001; J. G. Smith & McDowall, 2004; Stephan et al., 2011; Vandenbossche et al., 2009, 2013; Wilkinson et al., 2009).

sequential learning in participants with PD (J. G. Smith & McDowall, 2004; Westwater et al., 1998). These inconsistent results may indicate that motor sequence learning still affected the underlying sequence learning skill, because the verbal responses still comprised a motor sequence component (as the pronunciation of these words also consists of a motor sequence of speech movements). Moreover, the verbal responses were still relevant to the perceptual location of the stimuli, so perceptual and motor sequences remained correlated.

The latter is another important issue with the classical SRT-task; it does not allow a proper assessment of implicit sequence learning abilities independently from motor sequence learning. The task requires participants to respond to a sequence of perceptual visual stimuli with a sequence of corresponding motor responses, so perceptual and motor learning components of sequential skill learning are intertwined (see e.g. Deroost & Soetens 2006). Concluding that implicit sequence learning is deteriorated in patients with PD, when the assessment of learning depends on the integrity of sequential motor abilities might therefore be highly problematic. Imaging research, for instance, documents that motor sequence learning is subserved by at least partially different neural substrates than perceptual sequence learning (Gheysen et al., 2011; Rose et al., 2011). It is essential to gain insight in the exact underlying cognitive processes that are affected in sequential skill learning in PD, e.g. for treatment purposes, to finetune (cognitive) rehabilitation protocols or to target crucial cortical areas via non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) (Deroost et al., 2018; Firouzi et al., 2020).

Several studies have adapted the SRT-task in various ways, in an attempt to disconnect perceptual and motor learning components. Gamble et al. (2014), for instance, used an adapted version of the classic SRT-task (the 'Triplets Learning Task') to investigate sequential learning in individuals with PD and matched healthy controls (Gamble et al., 2014). Vakil and colleagues (2000) reduced the motor component in their adapted SRT-task by simplifying the response selection (i.e. choice between multiple keys on the keyboard) to a Go/No-Go task (i.e. "tap spacebar" or "do not tap

spacebar") (Vakil et al., 2000). In both studies, however, the sequence in which motor responses needed to be given was correlated with the perceptual sequence.

As aforementioned studies demonstrate, assessing sequential knowledge without inclusion of any type of sequential motor knowledge is rather challenging. Although previous studies tried to limit the motor component of the task, participants' motor responses to the target stimuli still followed a sequential order that was correlated to the perceptual sequence of the stimuli. The purpose of the present study was therefore to fully isolate implicit perceptual sequence learning from motor sequence learning, in order to provide more clarity on implicit sequential learning abilities in PD. We compared the performance of individuals with PD and age-matched healthy controls (HC) on a perceptual sequence learning task to test the hypothesis that implicit sequence learning² may be preserved in PD when assessed independently from motor sequence learning. To this end, we employed an adapted version of the SRT-task in which the only sequential regularity was embedded in the perceptual environment, and was independent of the motor response sequence. Although sequence learning was still expressed through motor responses in this adapted perceptual SRT-task, these motor responses were completely randomly determined (i.e., there was no fixed, predetermined sequence to them) and therefore, by definition, responses were uncorrelated with the perceptual locations of the stimuli. In this regard, and in contrast to aforementioned studies, 'sequence learning' in the present study could only take place by invoking perceptual sequential learning skills – and not be based on motor sequential learning skills.

If implicit sequence learning is preserved in PD, we expect a decline in RTs over the blocks of the perceptual SRT-task containing a regular, repeating sequence (secondary outcome: general learning effect) in both groups. Additionally, and crucially, we expect RTs to increase when the blocks containing the repeating sequence are interrupted by a block with a random sequence and decrease

² In this study, learning was defined as the acquisition of perceptual sequential knowledge based on (1) performance improvement during the course of practice (secondary outcome: general learning) and (2) this improvement remaining relatively stable after this period of practice is interrupted by a random sequence (primary outcome: sequence-specific learning). As previously mentioned, another definition of learning is based on a retention test (Edwards, 2010; Soderstrom & Bjork, 2015). In the present study, the aim was to investigate the acquisition of a novel perceptual sequence, and not the retention of said sequence.

once more when the repeating sequence is reintroduced (primary outcome: sequence-specific learning effect).

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2. METHODS

2.1. Participants

Twenty-two participants with PD, aged 50 to 80 years old, were classified Hoehn & Yahr stage II or III by a certified neurologist (Hoehn & Yahr, 1967). Nineteen healthy participants within the same age range were included as a control group, see Table 1.

Table 1 Demographical, neuropsychological and motor variables of participants

Variable	PD (n = 19)	HC (n = 18)	P
Gender (male:female)	10:9	6:12	.236
Age (years)	65.00 (60.25 – 69.75)	61.50 (56.76 – 66.24)	.368
Level of education* (1:2:3:4)	0:2:3:14	0:2:7:9	.197
Disease duration (months)	91.95 (57.57 – 126.33)		
Dominant hand (R:L)	19:0	17:1	.298
Most affected side (R:L:E)	7:5:7		
SCOPA-COG (0-39)	29.74 (27.38 – 28.95)	31.06 (28.89 – 33.22)	.393
MMSE (0-30)	28.37 (27.78 – 28.95)	29.50 (29.24 – 29.76)	.002
HADS			
Anxiety (0-21)	5.47 (4.25 – 6.70)	6.44 (4.99 – 7.89)	.287
Depression (0-21)	4.58 (3.18 – 5.98)	3.61 (2.00 – 5.22)	.277
UPDRS-III (0-56)	7.95 (5.01 – 10.89)		
Medication (D-A:D-P:D-I)	17:12:12		
LEDD	589.55 (420.33 – 758.78)		

Continuous variables are expressed as mean (95% CI).

* Level of education: based on an ordinal four-point scale: 1) primary school; 2) lower secondary education; 3) higher secondary education; 4) higher education.

Abbreviations: M, mean; SD, standard deviation; R, right; L, left; E, equal; SCOPA-COG, Scales for Outcomes in Parkinson's disease – COGNition; MMSE, Mini Mental State Examination; HADS, Hospital Anxiety and Depression Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; D-A, Dopamine receptor agonists; D-P, Dopamine precursors; D-I, Dopamine metabolism inhibitors (e.g. MAO-B, Monoamine oxidase B inhibitor); LEDD, Levodopa Equivalent Daily Dose; CI, Confidence Interval.

All participants had normal or corrected eyesight. Participants with PD were tested during the ON-phase of their medication. Participants were excluded from the study if they presented with signs of dementia, objectified by means of the <24/30 cut-off score on the Mini Mental State Examination (MMSE) (Kochhann et al., 2010). One individual with PD scored below the cut-off of 24/30 on the

MMSE, and was therefore excluded from the analyses and Table 1. Participants were also excluded from further data analyses if they scored minimally two standard deviations above their respective group average for (a) the total number of erroneous responses and/or (b) the total median RT of correct responses on the task. This resulted in three participants (one HC, two PD) being excluded from the study.

2.2. Perceptual Serial Reaction Time task

Participants' perceptual sequence learning was assessed by means of the perceptual SRT-task previously used by Coomans et al. (2011). See Figure 1 for a schematic representation of the task.

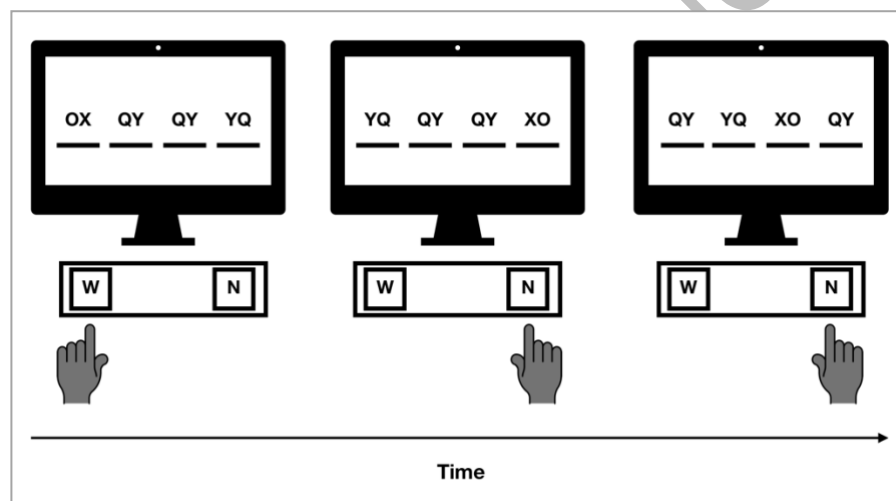


Fig. 1: Schematic representation of the perceptual SRT-task. On each trial, participants had to react as quickly as possible to the target stimulus identity by pressing the “W” key on an AZERTY-keyboard when the letter pair “OX” appeared (using their left index finger) and press the “N” key when the letter pair “XO” appeared (using their right index finger), or vice versa, as the stimulus-response mapping was counterbalanced between participants. Target letter pairs’ perceptual locations followed a sequence and were irrelevant for the randomly determined motor responses to the stimuli’s identities. In this example, the target appeared in locations “1”, “4”, “3”, ... respectively. Based on the stimulus identities “OX”, “XO”, “XO”, ... the participant responded with “W”, “N”, “N”, ... (in other words: “Left”, “Right”, “Right”, ...). Although these motor responses are linked to the stimulus identity, which was entirely randomly determined, they are completely independent of the stimulus locations which change sequentially. The perceptual location sequence is therefore de-coupled from the motor responses.

The perceptual SRT-task was carried out on a computer with 17-inch screen, using Psychology Software Tools’ E-prime® software (version 2.0). Participants were instructed to identify as quickly

and correctly as possible the target stimulus (letter pairs “OX” or “XO”), appearing in one of four locations and presented amongst three distractor stimuli (letter pairs “QY” or “YQ”) occupying the three remaining locations. The four stimulus letter pairs appeared horizontally aligned on the computer screen, with a distance of 3 cm between all pairs (3.44° visual angle from a viewing distance of 50 cm). Four black underlines of 1 cm wide, which remained on the screen during the blocks, marked the locations at which the letter pairs appeared and were presented 1.50 cm under the letter pairs (1.72° visual angle). All letter pairs were depicted in font arial, measuring 1 cm width x 1 cm height (1.15° visual angle). Participants had to press the “W” key on an AZERTY-keyboard when the letter pair “OX” appeared (using their left index finger) and press the “N” key when the letter pair “XO” appeared (using their right index finger), or vice versa, as the stimulus-response mapping was counterbalanced between participants. The letter pairs “XO” and “OX” were presented to each participant the same number of times (50% - 50%), each in a different random order.

In this adapted SRT-task, two stimulus features can be distinguished, namely (a) the identity of the target stimulus and (b) the location of the target stimulus. The identity of the target letter pairs (“XO” or “OX”) and of the distractors (“QY” or “YQ”) was entirely randomly defined for each location in each trial. Motor responses were linked to the stimulus identity and therefore also varied randomly. This means that, although participants still needed to provide motor responses, there was no predetermined sequence imposed to the motor responses. The location of the target letter pairs, however, did follow a predetermined first-order probabilistic sequence (Coomans et al., 2011; Soetens et al., 2004). Therefore, sequence learning of the target locations did not rely on motor sequential learning skills and could only take place by calling on perceptual sequential learning skills.

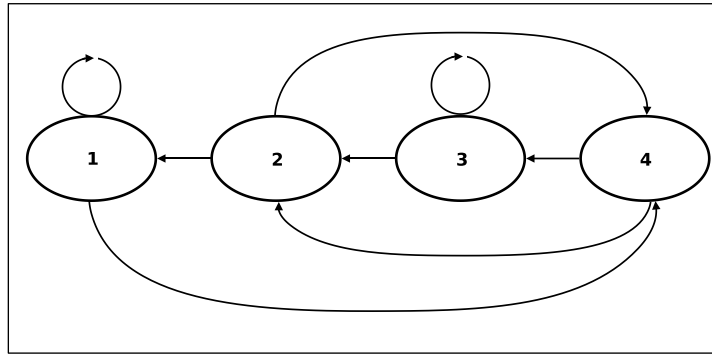


Fig. 2: A schematic reproduction of the probabilistic first-order sequence imposed on the target's location. The numbers refer to the screen locations, the arrows indicate the allowed location transitions. Taken from Coomans et al. (2011).

The target letter pair remained on screen until the participant pressed either one of the response keys. In other words, the next (i.e., new) target was presented irrespective of whether the response to the previous target was correct or erroneous. Participants were instantly made aware of an erroneous response by an auditory error message. They also received feedback regarding average response time and error rate after each block. The response-stimulus interval was held constant at 400 ms.

The experiment consisted of 12 blocks, each consisting of 100 trials. Following each block of trials, a 30 second break was provided, after which participants could start the next block by pressing the spacebar. In Blocks 1 through 10 and Block 12 of the actual experiment – unbeknown to the participants – the location of the target stimuli followed the probabilistic sequence. Note again that the structured perceptual location of the stimuli was entirely irrelevant for the random motor responses to the stimuli's identities, ensuring that the perceptual (location) and motor (identity) dimensions of the target were entirely uncorrelated. In Block 11 the predetermined probabilistic location sequence was replaced with a random sequence, in which target stimuli were presented at fully random locations. We expect participants' RTs to decline (i.e., react faster) if they implicitly learn the predetermined repeating location sequence in Blocks 1 through 10 and Block 12 (general learning effect). We also expect the RTs to suddenly increase (i.e., participants react slower) in random Block 11 and decrease once more in sequenced Block 12 (sequence-specific learning effect).

2.3. Experimental Procedure

Prior to the experimental procedure, participants' baseline characteristics such as gender, age, education level, dominant hand, disease duration (PD only), predominantly affected body side (PD only), medication type, dose and time of intake were queried. Afterwards, a neuropsychological screening was carried out in all participants (PD and HC), as previous studies showed that outcomes on motor and cognitive tests may significantly impact sequence learning in individuals with PD (Deroost et al., 2006; Ruitenberg et al., 2015; Stephan et al., 2011; Vandenbossche et al., 2009). The neuropsychological screening battery consisted of the Scales for Outcomes in Parkinson's Disease-Cognition (SCOPA-COG, designed specifically to assess cognitive deficits in individuals with PD) (Marinus et al., 2003); Mini Mental State Examination (MMSE, used as a screening tool for dementia) (Tombaugh & McIntyre, 1992) and Hospital Anxiety and Depression Scale (HADS, a two-dimension scale developed to identify depression and anxiety) (Johnson et al., 1995; Roberts et al., 2001). Part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III) was used to assess motor function in the participants with PD (Metman et al., 2004).

Participants completed the perceptual SRT-task individually in a silent room at home, under supervision of the experiment leader. Prior to the actual experiment, a practice block of 50 trials was presented, in which the location of the target pair was determined randomly in each trial. This practice block served solely to familiarize participants with the task. The actual 12-block perceptual SRT-task, consisting of 12 blocks of 100 trials, was carried out after a 30 second break following the practice block. A recognition task was completed after the experimental procedure to determine whether participants became explicitly aware of the perceptual location sequence, as spontaneous explicit awareness of the sequence may increase the magnitude of learning (Destrebecqz, 2004). The recognition task, used to determine explicit retrieval of the learned content, was based on the task used in a study by Deroost et al. (2012) (Deroost et al., 2012). During the recognition task, participants

were presented with the two successively presented target letter pairs, the same as used in the SRT-task (“OX” or “XO”), each pair appearing in one of four locations (e.g. a leftmost letter pair followed by a leftmost letter pair; a leftmost letter pair followed by a left letter pair; ...). Each of the pairs was presented for 1000 ms, with an interstimulus interval of 1000 ms. Participants were instructed to ignore the identity of the target pair, which changed randomly in the recognition task, and to focus on the succession of locations of the pairs. After presentation of two successively presented letter pairs, participants had to indicate whether the succession of locations was recognized as predominant in the previously completed experiment, by pressing “Z” on the keyboard in case of a recognized location transition and “N” in case of an unrecognized location transition. No time limit was imposed on the response time and no feedback was given about judgment accuracy. In total, participants judged all 16 possible first-order location transitions (appearing in a random order) of which eight belonged to the probabilistic sequence structure and eight did not. In addition to the recognition task, participants were queried whether they were aware that most blocks contained a predetermined, repeating sequence. The duration of each test session was approximately 90 minutes.

2.4. Outcome Measures and Statistical Analysis

All statistical analyses were carried out using SPSS (IBM SPSS Statistics 26) and were two-tailed, with the level of significance set at $\alpha = 0.05$. Cohen’s f effect sizes are reported, with values of .10, .25, and .40 representing small, medium, and large effect sizes, respectively (Salkind, 2010).

2.4.1. Baseline data

Independent Samples T-tests (or non-parametrical alternative: Mann-Whitney U-test) and Chi-square Tests were carried out to determine differences between the PD and HC group’s baseline characteristics (gender, age, education level, dominant hand, disease duration (PD only), predominantly affected body side (PD only), medication type, dose and time of intake) and scores on the SCOPA-COG, MMSE, HADS and UPDRS-III (PD only).

2.4.2. Response times (RTs)

Response times were defined as the time between the presentation of the target letter pair on the computer screen and the effector pressing the response button. The analyses of the SRT-task performance were based on median RTs per block rather than mean RTs to minimize potential outlier effects. Practice trials, the first response after each break, erroneous responses and responses following an error were excluded from the RT analyses. In total, 5.65% of the data was discarded from the RT analyses (7.66% of the PD group, 3.53% of the HC group). Median RTs per block were analyzed to determine (1) a general learning effect (secondary outcome measure) and (2) a sequence-specific learning effect (primary outcome measure).

General learning effects were derived from a decline in median RTs over the 11 regularly sequenced blocks (i.e. Blocks 1-10, Block 12). A mixed factorial 11 x 2 repeated measures ANOVA was carried out with Block (11 levels: Blocks 1-10, Block 12) as within-subjects factor and Group (2 levels: PD, HC) as between-subjects factor. Conditions for this ANOVA model were checked by means of the one-sample Kolmogorov-Smirnov test and Mauchly's test. Since the assumption of normality was violated, the natural logarithm (i.e. transformation of data to correct this violation and improve linear fit overall) of the data was used (LN). The natural log transformation of the original data does not affect the interpretation of results: longer RTs correspond to higher logarithms of RTs and shorter RTs correspond to lower logarithms of RTs. Following logarithmic transformation, the one-sample Kolmogorov-Smirnov test indicated that there was no evidence to reject the assumption of normality of variables ($p > .100$ in both groups, in all blocks). As conditions for sphericity were not met, a correction based on the Huynh-Feldt coefficient was required. Polynomial contrasts were calculated to determine whether the decrease in median RTs showed a specific trend.

Sequence-specific learning effects were analyzed by means of a mixed factorial 2 x 2 repeated measures ANOVA with Block (2 levels: random Block 11, mean of adjacent sequenced Blocks 10 and

12) as within-subjects factor and Group (2 levels: PD, HC) as between-subjects factor. Once more, natural logarithms of median RTs were used, in order to meet the assumption of normality. After the logarithmic transformation (LN) of the median RT within the random block and the mean of the median RTs of the two surrounding blocks, a one-sample Kolmogorov-Smirnov test revealed no evidence to reject the assumption of normality of variables ($p > .200$ in both groups, for both variables). Mauchly's test showed that assumptions of sphericity were met.

2.4.3. Errors

To determine whether error percentages between both groups (PD, HC) differed significantly, a Mann-Whitney U-test was carried out. This non-parametrical alternative to the Independent Samples T-test was used as the Shapiro-Wilk test revealed that the total number of errors in the PD group was not normally distributed.

2.4.4. Sequence awareness

For the analysis of the post-experiment recognition task, a measure of recognition discriminability (sensitivity measure d') was calculated to determine participants' judgment accuracy of first-order location transitions. When the proportion of erroneous responses exceeds or equals the proportion of accurate responses, the d' value is negative or equal to zero, indicating that judgment performance is at chance level (Macmillan & Creelman, 2004). In contrast, a positive d' indicates good recognition discriminability, with higher positive d' values suggesting higher likelihood that participants possessed conscious awareness of the sequence transitions (Deroost et al., 2012). One Sample t-Tests were carried out to assess whether mean d' s differed significantly from zero. Correlations between the amount of explicit sequence awareness (as measured by d') and the degree of perceptual sequence learning were analyzed. In addition, we reran the ANOVA analyses for determining learning effects, but with d' as a covariate to further determine whether explicit sequence awareness influenced learning effects.

2.4.5. Correlation between perceptual sequence learning and other variables

Correlation analyses were performed to determine whether the degree of perceptual sequence learning was correlated with baseline demographic (age, gender, disease duration, education level), cognitive (MMSE and SCOPA-COG scores), emotional (HADS) and/or motor (UPDRS-III) characteristics, sequence awareness and medication type and dosage. If assumptions for parametrical testing were met, Pearson's correlation coefficients were calculated. If assumptions were violated, the non-parametrical alternative – Spearman's rank correlation coefficient – was applied. Bonferroni corrections were applied to the original α -value (0.05), to adjust for multiple pairwise comparisons (resulting in a significance level set at $p < .0055$).

3. RESULTS

3.1 Participants

Baseline demographical characteristics, neuropsychological and clinical variables of 19 participants with PD (mean age 65 ± 9.85 ; 9 women) and 18 healthy controls (mean age 61.5 ± 9.54 ; 12 women) are summarized in Table 1.

3.2 Outcome Measures

3.2.1. General learning effects

There was a significant main effect of the within-subjects factor “Block” $F(2.506, 87.714) = 46.876, p < .001, \eta p^2 = .573$, indicating a significant difference in the logarithms of median RTs across the blocks containing a sequence. Based on the sample mean values per block, a decreasing trend (i.e. “reacted faster”) could be observed as the blocks progressed and this trend was found to be significantly linear $F(1, 35) = 91.083, p < .001$. Although logarithms of median RTs were lower (i.e. “reacted faster”) in the HC group compared to the PD group, the main effect of between-subjects factor “Group” failed to reach statistical significance $F(1, 35) = 3.196, p = .082$. No significant interaction effects were found between “Group” and “Block” $F(1, 35) = .541, p = .467$.

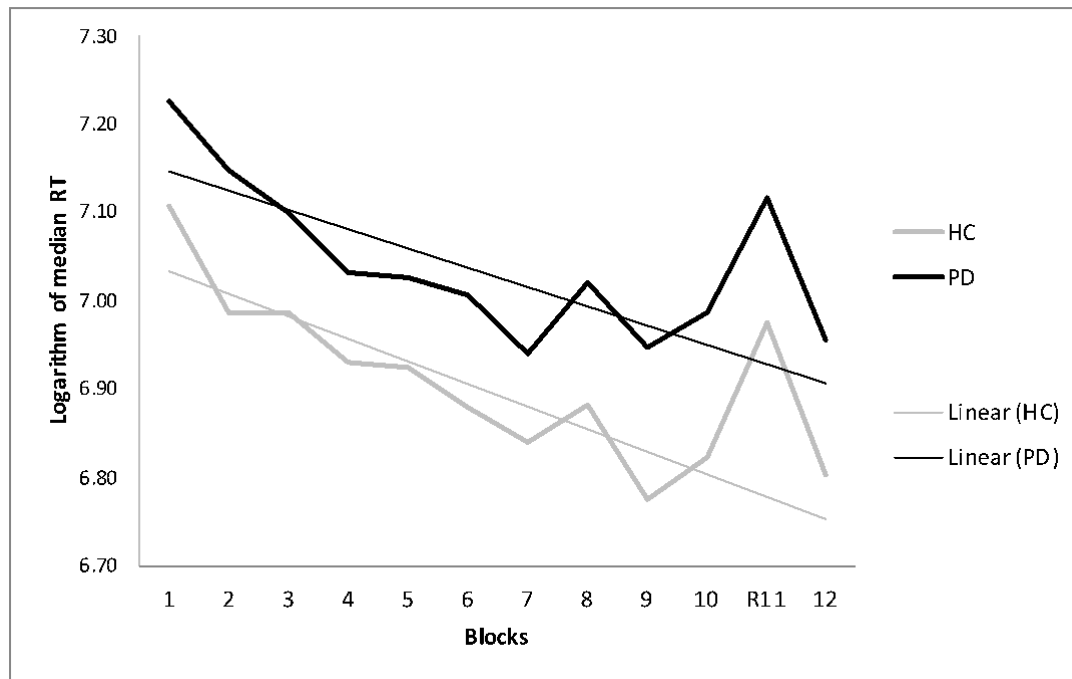


Fig. 3: Logarithms of median RTs (y-axis) for each experimental block (x-axis), for both groups: PD group in grey, HC group in black. Logarithmic transformation of original RT data did not affect the interpretation of results: longer RTs correspond to higher logarithms of RTs and shorter RTs correspond to lower logarithms of RTs. Regression lines for sequential blocks, representing the linear decrease in (logarithms of) median RTs, as a measure of general learning effects for both groups: Linear (HC) for HC group, Linear (PD) for PD group. Abbreviations: RT Response Time, HC Healthy Controls, PD Parkinson's Disease.

3.2.2. Sequence-specific learning effects

There was a significant and strong main effect of within-subjects factor "Block" $F(1, 35) = 196.456, p < .001, \eta p^2 = .849$. The logarithms of median RTs in random Block 11 were higher than the mean logarithm of median RTs in the two neighboring (regularly sequenced) Blocks 10 and 12, showing significant location sequence learning took place, see Figure 3. A significant, moderate main effect of the between-subjects factor "Group" was also observed $F(1, 35) = 4.747, p = .036, \eta p^2 = .119$, showing that logarithms of the median RTs of the HC group were lower than of the PD group, see Figure 3. Importantly, no significant interaction-effect was found between "Block" and "Group" $F(1, 35) = .621, p = .436$, revealing that sequence-specific learning was not significantly different between

the HC ($M = 173.94 \pm 52.42$ SD) and PD groups ($M = 156.53 \pm 104.16$ SD) (difference scores of the sequential learning effect; random – sequenced)³.

3.2.3. Post-hoc Bayesian analysis of sequence-specific learning effects

Analyses of the SRT-task did not yield a significant difference in implicit perceptual location sequence learning between the PD and HC groups. We subsequently calculated a post-hoc Bayes factor to determine whether the abovementioned insignificant interaction-effect between “Block” and “Group” could be interpreted as evidence for the absence of a difference in sequence-specific perceptual learning between the PD and HC groups. The null-hypothesis (H_0) was defined as no significant difference in learning between the PD and HC groups, whereas the alternate hypothesis (H_1) suggested a significant difference in learning. The Bayes factor amounted to $B_{01} = 3.543$ (i.e., $B_{10} = .282$) (mean difference = 16.5117, 95% credible interval -39.51-72.53), indicating that the null hypothesis H_0 is a 3.543 times more probable explanation for the data than the alternate hypothesis H_1 . Our Bayes factor of $B_{01} = 3.543$ can therefore be considered as substantial evidence for the null hypothesis (Dienes, 2014), confirming that the difference in sequence-specific perceptual learning between the PD and HC group was not significant.

3.2.4. Errors

A non-parametrical Mann-Whitney U-test revealed that the PD group had a significantly higher number of errors on the perceptual SRT-task ($M = 39.95$, $SD = 43.519$) compared to the HC group ($M = 13.95$, $SD = 6.881$), $U = 101$, $p = .033$. Correlational analyses did not reveal any significant, negative correlations between RTs and the number of errors on the task, indicating no significant speed-accuracy trade-off at the participant level.

³ There were no significant interactions of “disease-most-affected side” (PD only) nor “dominant hand” with the main effect of “Block” (all p 's > .05). This indicates that sequence-specific learning still occurred regardless of which side was most affected in the individuals with PD, and regardless of participants' dominant hand.

3.2.5. Sequence awareness

Median d' s were $.00 \pm 0.68$ SD and $.00 \pm 0.73$ SD for the PD and HC groups, respectively. One-Sample t-Tests revealed that mean d' s did not differ significantly from zero, $p = .206$ and $p = .783$ for the respective PD and HC groups. In addition, a Kruskal Wallis test showed that median d' s did not differ between groups, $p = .401$. No significant correlations between d' and the degree of perceptual sequence learning were revealed in either group (see Table 2). No significant interaction of sensitivity measure d' as covariate (in the 2×2 repeated measures ANOVA for analysis of sequence-specific learning effects) was observed with the main effect of "Block" $F(1, 34) = .234, p = .632$. These outcomes suggest that there was no significant explicit awareness of the sequence in either of the groups.

3.2.6. Correlation between perceptual sequence learning and other variables

Correlations between the degree of perceptual sequence learning with demographic, cognitive, emotional and motor variables per group are displayed in Table 2. Bonferroni corrections were applied to the original α -value (0.05) to adjust for multiple pairwise comparisons (resulting in a significance level set at $p < .0055$), after which none of the variables correlated significantly with perceptual sequence learning.

Table 2 Correlation between perceptual sequence learning and other variables

Variable	PD (n = 19)		HC (n = 18)	
	Correlation with PSQ	p	Correlation with PSQ	p
Age	.33°	.165	.17°	.513
Gender	-.058°	.814	-.568°	.014
Education level	-.33°	.162	-.18°	.477
Disease duration	.00°	.991		
SCOPA-COG	-.33°°	.167	.27°°	.288
HADS-Anxiety	.12°°	.639	-.45°°	.058
HADS-Depression	.07°	.764	.19°	.449
MMSE	-.450°	.053	.225°	.370
UPDRS-III	.09°	.706		
Explicit awareness (d')	.265°	.273	-.076°	.766
Medication type	-.391°	.098		
LEDD	.118°	.629		

Abbreviations: PD, Parkinson's Disease; HC, Healthy Controls; PSQ, Perceptual Sequence Learning; p, significance value; SCOPA-COG, Scales for Outcomes in Parkinson's Disease-Cognition; HADS, Hospital Anxiety and Depression Scale; MMSE, Mini Mental State Examination; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; LEDD, Levodopa Equivalent Daily Dose

° Spearman's correlation coefficient rho (ρ)

°° Pearson's correlation coefficient r (r)

4. DISCUSSION

The aim of this study was to assess sequence learning abilities in PD independently from motor sequence learning. This was done by using a perceptual SRT-task without a sequential motor component. Meta-analyses systematically indicate an impaired acquisition of sequential knowledge in patients with PD (Clark & Lum, 2017; Hayes et al., 2015; Siegert et al., 2006). However, results of some studies investigating motor sequence learning are often cited as evidence supporting or refuting an impairment in the underlying sequence learning ability, without further defining the specific type of learning (Deroost et al., 2006; Ferraro et al., 1993; Kelly et al., 2004; Seidler et al., 2007; Vandenbossche et al., 2013). In this respect, drawing conclusions regarding implicit sequence learning in patients with PD when the assessment of learning depends on the integrity of sequential motor abilities might be problematic.

Therefore, in the present study, implicit non-motor sequence learning abilities were measured by means of a perceptual SRT-task based on the design of Coomans et al. (2011). Crucially, and in contrast to previous adaptations of the SRT-task (Gamble et al., 2014; J. Smith et al., 2001; J. G. Smith & McDowall, 2004; Vakil et al., 2000; Westwater et al., 1998), motor responses were randomly determined for each location, and thus entirely independent of the perceptual location sequence. This allowed us to estimate (perceptual) sequential knowledge acquisition independently from motor sequence learning. In other words, 'sequence learning' in the present study could only take place by invoking perceptual sequential learning skills – and not by relying on motor sequential learning skills.

Our results indicate that the PD group displayed preserved implicit perceptual sequence learning abilities. Both the PD and HC groups showed the same overall linear decreasing trend in median RTs with repetition of the sequence throughout Blocks 1-10 and 12, indicating a general learning effect. More importantly, irrespective of group, median RTs in random Block 11 increased

compared to the two surrounding sequenced Blocks 10 and 12 (sequence-specific learning effect).⁴ These findings suggest that implicit sequence learning – as measured by a perceptual SRT-task – was not affected in our sample of individuals with PD and even comparable to healthy individuals. Overall differences in RT performance between the PD and HC group did not reach statistical significance, although patients committed significantly more errors.

Accordingly, our findings indicate that previous studies reporting impaired implicit sequence learning in participants with PD, derived from attenuated motor sequence learning abilities, do not allow to conclude that sequence learning abilities per se are compromised (Deroost et al., 2006; Ferraro et al., 1993; Kelly et al., 2004; Seidler et al., 2007; Vandenberg et al., 2013). The current findings instead support the assumption that the reported deficits in implicit sequence learning in individuals with PD are likely due to deficiencies in general motor function or implicit motor sequence learning, rather than impairments in the underlying implicit sequence learning ability itself.

One possible explanation for the differential impact of PD on implicit perceptual versus motor sequence learning, is that they may not rely on the same basal ganglia-thalamocortical structures. Rose et al. (2011), for instance, designed a purely perceptual and a purely motor variant of the SRT-task to investigate whether the neural mechanisms involved in perceptual sequence learning differ from those involved in motor sequence learning. Their fMRI study in healthy individuals indeed revealed a functional differentiation of learning-related brain structures, as bilateral hippocampal activation was observed only for implicit learning of the perceptual sequence, and not of the motor sequence (Rose et al., 2011). Moreover, an enhanced recruitment of the basal ganglia and motor cortex was reported for motor sequence learning as compared to perceptual sequence learning. This suggests that both types of sequence learning invoke different neural structures. More research is needed to determine whether differential neural mechanisms involved in motor and perceptual sequence learning might explain preserved perceptual sequence learning in PD.

⁴ Although overall scores may be similar across groups, the variability that is seen over time as reflected in the standard deviation scores may be different and clinically relevant. However, a replication of the repeated measures ANOVA analyses with standard deviations of RTs (instead of median RTs) as dependent variable revealed no significant effects (all $ps > .05$).

A few limitations of the current study should be considered in future research. First, although there was no correlation between participants' motor responses and the perceptual visual sequence in this study, sequence learning was still expressed through motor responses in the employed SRT-task. To the best of our knowledge, however, no better behavioral measure of sequential learning exists than response times and accuracy-based measures (Urry et al., 2015).

Secondly, it is unclear to what extent our findings can be generalized to the population of individuals with PD. The sample included in this study did not present significant cognitive impairments and were classified as Hoehn & Yahr stage II or III (i.e., the mid-stages of the disease according to this primarily motor-oriented classification scale). Conducting a similar study in a more cognitively impaired sample of patients with PD, or patients in a more advanced stage of the disease would be an interesting avenue for future research.

Another limitation is that the post-hoc Bayes factor calculation was based on effect sizes of the current study, and not of previous research. We did not use the effect size as determined in previous studies as perceptual sequence learning in those studies was not independent of motor sequence learning and therefore not considered sufficiently comparable to the current study.

A fourth limitation is that the manipulation of medication status (i.e., ON medication vs. OFF medication) was not included as a factor in the study design as all participants with PD were tested while on their dopamine-replacing medication. Associations between medication type, dosage and the amount of learning were, however, assessed post-hoc and were insignificant. In their State-of-the-Art, Ruitenberg and colleagues (2015) suggest that dopaminergic medication may enhance particular (motor-related) processes involved in sequence learning, but hinder other (cognition-related) processes that are still intact in PD. For instance, evidence suggests that sequential learning may actually be impaired when patients are on dopaminergic medication (Kwak et al., 2010, 2012; Ruitenberg et al., 2015). Kwak and colleagues suggest that dopaminergic medication may particularly impair early phases of sequence learning, in which performance is more cognitively controlled as opposed to later phases in which performance is more automatized on the basis of motor

representations. As we only assessed participants' performance on the SRT-task during the early, pre-automatized phase of learning a novel sequence, performance on the task was indeed more cognitively controlled. According to aforementioned studies, one could hypothesize that the dopaminergic medication would therefore have negatively impacted the performance of participants with PD. However, this was not the case, as our findings indicate preserved perceptual sequence learning in these individuals. Furthermore, Kwak and colleagues used an explicit motor sequence learning task, whereas the present study investigated implicit perceptual sequence learning abilities. It is unclear as of yet whether the effects of dopaminergic medication also hold true for implicit sequence learning.

A fifth limitation is that we cannot determine to what extent learning relied on additional, intact compensatory pathways, as we did not employ any neural measures such as functional Magnetic Resonance Imaging (fMRI). In recent years, evidence has accumulated that the cerebellum may play a pathological as well as a compensatory role in PD (Tao Wu & Hallett, 2013), as interconnections between the cerebellum, basal ganglia (as key pathophysiological area of PD) and the cortex have been established at cortical and subcortical levels (Bostan & Strick, 2018). Although it is known that the cerebellum is involved in the initial, rapid phase of implicit and explicit motor sequence learning, it is still unclear whether this (cortico-)cerebellar pathway may also play a compensatory role in perceptual sequence learning in PD (Bostan & Strick, 2018; Doyon et al., 2003).

Finally, the present study only investigated the acquisition of perceptual sequence learning, as participants carried out the task just once. Future research should investigate the consolidation of this skill on the short and longer term, as well as transfer effects on (e.g. more functional) learning tasks other than the perceptual SRT-task, as these are vital for the successful functional rehabilitation of individuals with PD.

CONCLUSION

In conclusion, the present study suggests that implicit sequence learning may be preserved in individuals in the mid stages of PD when assessed independently from motor sequence learning. In this sample of individuals with PD, sequential learning skill even proved comparable to that of matched, healthy individuals. Our findings suggest that previous findings reporting impaired implicit sequence learning in individuals with PD could be attributed to compromised motor sequence learning abilities. Additional research is needed to confirm these findings in a more cognitively impaired sample of individuals with PD and patients in a more advanced stage of the disease. A comparison between patients ON and OFF dopaminergic medication would also provide valuable information. Future neuroimaging research should address potential compensatory neural pathways activated during perceptual sequence learning in PD.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

- Aarsland, D., Brønnick, K., Larsen, J. P., Tysnes, O. B., & Alves, G. (2009). Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. *Neurology*, 72(13), 1121–1126.
- Aarsland, D., Brønnick, K., Williams-Gray, C., Weintraub, D., Marder, K., Kulisevsky, J., Burn, D., Barone, P., Pagonabarraga, J., & Allcock, L. (2010). Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. *Neurology*, 75(12), 1062–1069.
- Bostan, A. C., & Strick, P. L. (2018). The basal ganglia and the cerebellum: nodes in an integrated network. *Nature Reviews Neuroscience*, 19(6), 338. <https://doi.org/10.1038/s41583-018-0002-7>
- Clark, G. M., & Lum, J. A. G. G. (2017). Procedural learning in Parkinson's disease, specific language impairment, dyslexia, schizophrenia, developmental coordination disorder, and autism spectrum disorders: A second-order meta-analysis. *Brain and Cognition*, 117(July), 41–48. <https://doi.org/10.1016/j.bandc.2017.07.004>
- Clark, G. M., Lum, J. A. G., & Ullman, M. T. (2014). A meta-analysis and meta-regression of serial reaction time task performance in Parkinson's disease. *Neuropsychology*, 28(6), 945.
- Coomans, D., Deroost, N., Zeischka, P., & Soetens, E. (2011). On the automaticity of pure perceptual sequence learning. *Consciousness and Cognition*, 20(4), 1460–1472.
- Dauer, W., & Przedborski, S. (2003). Parkinson's Disease: Mechanisms and Models. *Neuron*, 39(6), 889–909. [https://doi.org/https://doi.org/10.1016/S0896-6273\(03\)00568-3](https://doi.org/https://doi.org/10.1016/S0896-6273(03)00568-3)
- Deroost, N., Baetens, K., Jochen, V., Kerckhofs, E., Vandenbossche, J., & Kerckhofs, E. (2018). Anodal tDCS of the Primary Motor Cortex and Motor Sequence Learning in a Large Sample of Patients with Parkinsons Disease. *Neuropsychiatry*, 8(1), 35–46. <https://doi.org/10.4172/neuropsychiatry.1000323>

- Deroost, N., Kerckhofs, E., Coene, M., Wijnants, G., & Soetens, E. (2006). Learning sequence movements in a homogenous sample of patients with Parkinson's disease. *Neuropsychologia*, 44(10), 1653–1662. <https://doi.org/10.1016/j.neuropsychologia.2006.03.021>
- Deroost, N., Vandenbossche, J., Zeischka, P., Coomans, D., & Soetens, E. (2012). Cognitive control: A role for implicit learning? *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 38(5), 1243.
- Destrebecqz, A. (2004). The effect of explicit knowledge on sequence learning: A graded account. *Psychologica Belgica*, 44, 217–248. <https://doi.org/10.5334/pb-44-4-217>
- Dickson, D. W. (2018). Neuropathology of Parkinson disease. *Parkinsonism & Related Disorders*, 46, S30–S33.
- Dienes, Z. (2014). Using Bayes to get the most out of non-significant results. *Frontiers in Psychology*, 5, 781.
- Dominey, P. F., Ventre-Dominey, J., Broussolle, E., & Jeannerod, M. (1997). Analogical transfer is effective in a serial reaction time task in Parkinson's disease: Evidence for a dissociable form of sequence learning. *Neuropsychologia*, 35(1), 1–9. [https://doi.org/10.1016/S0028-3932\(96\)00050-4](https://doi.org/10.1016/S0028-3932(96)00050-4)
- Dorsey, E., Sherer, T., Okun, M. S., & Bloem, B. R. (2018). The emerging evidence of the Parkinson pandemic. *Journal of Parkinson's Disease*, 8(s1), S3–S8.
- Doyon, J., Penhune, V., & Ungerleider, L. G. (2003). Distinct contribution of the cortico-striatal and cortico-cerebellar systems to motor skill learning. *Neuropsychologia*, 41(3), 252–262. [https://doi.org/10.1016/S0028-3932\(02\)00158-6](https://doi.org/10.1016/S0028-3932(02)00158-6)
- Draijer, W., Eizenga, W., & Sluiter, A. (2011). NHG-STANDAARD-Ziekte van Parkinson. *Huisarts En Wetenschap*, 54(7), 380.
- Edwards, W. H. (2010). *Motor learning and control: From theory to practice*. Cengage Learning.

- Fearnley, J. M., & Lees, A. J. (1991). AGEING AND PARKINSON'S DISEASE: SUBSTANTIA NIGRA REGIONAL SELECTIVITY. *Brain*, 114(5), 2283–2301. <https://doi.org/10.1093/brain/114.5.2283>
- Ferraro, F. R., Balota, D. A., & Connor, L. T. (1993). Implicit memory and the formation of new associations in nondemented parkinson's disease individuals and individuals with senile dementia of the alzheimer type: A serial reaction time (SRT) investigation. *Brain and Cognition*, 21(2), 163–180. <https://doi.org/10.1006/brcg.1993.1013>
- Firouzi, M., Van Herk, K., Kerckhofs, E., Swinnen, E., Baeken, C., Van Overwalle, F., & Deroost, N. (2020). Transcranial direct-current stimulation enhances implicit motor sequence learning in persons with Parkinson's disease with mild cognitive impairment. *Journal of Neuropsychology*, n/a(n/a). <https://doi.org/https://doi.org/10.1111/jnp.12231>
- Foltynie, T., Brayne, C. E. G., Robbins, T. W., & Barker, R. A. (2004). The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain*, 127(3), 550–560.
- Gamble, K. R., Cummings Jr, T. J., Lo, S. E., Ghosh, P. T., Howard Jr, J. H., & Howard, D. V. (2014). Implicit sequence learning in people with Parkinson's disease. *Frontiers in Human Neuroscience*, 8, 563.
- Gheysen, F., Van Opstal, F., Roggeman, C., Van Waelvelde, H., & Fias, W. (2011). The neural basis of implicit perceptual sequence learning. *Frontiers in Human Neuroscience*, 5, 137.
- Giordano, N., Iemolo, A., Mancini, M., Cacace, F., De Risi, M., Latagliata, E. C., Ghiglieri, V., Bellenchi, G. C., Puglisi-Allegra, S., & Calabresi, P. (2017). Motor learning and metaplasticity in striatal neurons: relevance for Parkinson's disease. *Brain*, 141(2), 505–520.
- Gobel, E. W., Blomeke, K., Zadikoff, C., Simuni, T., Weintraub, S., & Reber, P. J. (2013). Implicit perceptual-motor skill learning in mild cognitive impairment and Parkinson's disease. *Neuropsychology*, 27(3), 314.
- Hashemirad, F., Zoghi, M., Fitzgerald, P. B., & Jaberzadeh, S. (2016). The effect of anodal transcranial direct current stimulation on motor sequence learning in healthy individuals: A systematic

- review and meta-analysis. *Brain and Cognition*, 102, 1–12.
<https://doi.org/10.1016/j.bandc.2015.11.005>
- Hayes, H. A., Hunsaker, N., & Dibble, L. E. (2015). Implicit Motor Sequence Learning in Individuals with Parkinson Disease: A Meta-Analysis. *Journal of Parkinson's Disease*, 5(3), 549–560.
<https://doi.org/10.3233/JPD-140441>
- Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: onset, progression, and mortality. *Neurology*, 17(5), 427.
- Horiba, M., Ueki, Y., Nojima, I., Shimizu, Y., Sahashi, K., Itamoto, S., Suzuki, A., Yamada, G., Matsukawa, N., & Wada, I. (2019). Impaired Motor Skill Acquisition Using Mirror Visual Feedback Improved by Transcranial Direct Current Stimulation (tDCS) in Patients With Parkinson's Disease. *Frontiers in Neuroscience*, 13, 602.
<https://doi.org/10.3389/fnins.2019.00602>
- Jackson, G. M., Jackson, S. R., Harrison, J., Henderson, L., & Kennard, C. (1995). Serial reaction time learning and Parkinson's disease: Evidence for a procedural learning deficit. *Neuropsychologia*, 33(5), 577–593.
- Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. *Journal of Neurology, Neurosurgery & Psychiatry*, 79(4), 368–376. <https://doi.org/10.1136/jnnp.2007.131045>
- Janvin, C., Aarsland, D., Larsen, J. P., & Hugdahl, K. (2003). Neuropsychological profile of patients with Parkinson's disease without dementia. *Dementia and Geriatric Cognitive Disorders*, 15(3), 126–131.
- Johnson, G., Burvill, P. W., Anderson, C. S., Jamrozik, K., Stewart-Wynne, E. G., & Chakera, T. M. H. (1995). Screening instruments for depression and anxiety following stroke: experience in the Perth community stroke study. *Acta Psychiatrica Scandinavica*, 91(4), 252–257.
<https://doi.org/10.1111/j.1600-0447.1995.tb09778.x>
- Kelly, S. W., Jahanshahi, M., & Dirnberger, G. (2004). Learning of ambiguous versus hybrid sequences

- by patients with Parkinson's disease. *Neuropsychologia*, 42(10), 1350–1357.
- Kochhann, R., Varela, J. S., Lisboa, C. S. de M., & Chaves, M. L. F. (2010). The Mini Mental State Examination: Review of cutoff points adjusted for schooling in a large Southern Brazilian sample. *Dementia & Neuropsychologia*, 4(1), 35–41. <https://doi.org/10.1590/S1980-57642010DN40100006>
- Kwak, Y., Müller, M. L. T. M., Bohnen, N. I., Dayalu, P., & Seidler, R. D. (2012). L-DOPA changes ventral striatum recruitment during motor sequence learning in Parkinson's disease. *Behavioural Brain Research*, 230(1), 116–124.
- Kwak, Y., Müller, M. L. T. M. T. M., Bohnen, N. I., Dayalu, P., & Seidler, R. D. (2010). Effect of dopaminergic medications on the time course of explicit motor sequence learning in Parkinson's disease. *Journal of Neurophysiology*, 103(2), 942–949. <https://doi.org/10.1152/jn.00197.2009>
- Lang, A. E., & Lozano, A. M. (1998). Parkinson's disease. First of two parts. *N Engl J Med*, 339(15), 1044–1053. <https://doi.org/10.1056/NEJM199810083391506>
- Lebouvier, T., Chaumette, T., Paillusson, S., Duyckaerts, C., Bruley des Varannes, S., Neunlist, M., & Derkinderen, P. (2009). The second brain and Parkinson's disease. *European Journal of Neuroscience*, 30(5), 735–741.
- Macmillan, N. A., & Creelman, C. D. (2004). *Detection theory: A user's guide*. Psychology press.
- Mamikonyan, E., Moberg, P. J., Siderowf, A., Duda, J. E., Have, T. Ten, Hurtig, H. I., Stern, M. B., & Weintraub, D. (2009). Mild cognitive impairment is common in Parkinson's disease patients with normal Mini-Mental State Examination (MMSE) scores. *Parkinsonism & Related Disorders*, 15(3), 226–231. <https://doi.org/https://doi.org/10.1016/j.parkreldis.2008.05.006>
- Marinus, J., Visser, M., Verwey, N. A., Verhey, F. R. J., Middelkoop, H. A. M., Stiggelbout, A. M., & van Hilten, J. J. (2003). Assessment of cognition in Parkinson's disease. *Neurology*, 61(9), 1222 LP – 1228. <https://doi.org/10.1212/01.WNL.0000091864.39702.1C>

- Mathys, C., Caspers, J., Langner, R., Sudmeyer, M., Grefkes, C., Reetz, K., Moldovan, A. S., Michely, J., Heller, J., Eickhoff, C. R., Turowski, B., Schnitzler, A., Hoffstaedter, F., & Eickhoff, S. B. (2016). Functional Connectivity Differences of the Subthalamic Nucleus Related to Parkinson's Disease. *Hum Brain Mapp*, 37(3), 1235–1253. <https://doi.org/10.1002/hbm.23099>
- Metman, L. V., Myre, B., Verwey, N., Hassin-Baer, S., Arzbaecher, J., Sierens, D., & Bakay, R. (2004). Test–retest reliability of UPDRS-III, dyskinesia scales, and timed motor tests in patients with advanced Parkinson's disease: An argument against multiple baseline assessments. *Movement Disorders*, 19(9), 1079–1084. <https://doi.org/10.1002/mds.20101>
- Muslimović, D., Post, B., Speelman, J. D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology*, 65(8), 1239–1245.
- Nissen, M. J., & Bullemer, P. (1987). Attentional requirements of learning: Evidence from performance measures. *Cognitive Psychology*, 19(1), 1–32. [https://doi.org/10.1016/0010-0285\(87\)90002-8](https://doi.org/10.1016/0010-0285(87)90002-8)
- Packard, M. G., & Knowlton, B. J. (2002). Learning and memory functions of the basal ganglia. *Annual Review of Neuroscience*, 25(1), 563–593.
- Pagonabarraga, J., & Kulisevsky, J. (2012). Cognitive impairment and dementia in Parkinson's disease. *Neurobiology of Disease*, 46(3), 590–596.
- Roberts, S. B., Bonnici, D. M., Mackinnon, A. J., & Worcester, M. C. (2001). Psychometric evaluation of the Hospital Anxiety and Depression Scale (HADS) among female cardiac patients. *British Journal of Health Psychology*, 6(4), 373–383. <https://doi.org/10.1348/135910701169278>
- Rose, M., Haider, H., Salari, N., & Büchel, C. (2011). Functional dissociation of hippocampal mechanism during implicit learning based on the domain of associations. *Journal of Neuroscience*, 31(39), 13739–13745.
- Ruitenbergh, M. F. L., Duthoo, W., Santens, P., Notebaert, W., & Abrahamse, E. L. (2015). Sequential movement skill in Parkinson's disease: A state-of-the-art. *Cortex*, 65, 102–112.

<https://doi.org/10.1016/j.cortex.2015.01.005>

Salkind, N. (2010). *Encyclopedia of Research Design*. <https://doi.org/10.4135/9781412961288> NV - 0

Savic, B., & Meier, B. (2016). How Transcranial Direct Current Stimulation Can Modulate Implicit Motor Sequence Learning and Consolidation: A Brief Review . *Frontiers in Human Neuroscience* , 10, 26. <https://doi.org/10.3389/fnhum.2016.00026>

Seidler, R. D., Tuite, P., & Ashe, J. (2007). Selective impairments in implicit learning in Parkinson's disease. *Brain Research*, 1137(1), 104–110. <https://doi.org/10.1016/j.brainres.2006.12.057>

Siegert, R. J., Taylor, K. D., Weatherall, M., & Abernethy, D. A. (2006). Is implicit sequence learning impaired in Parkinson's disease? A meta-analysis. *Neuropsychology*, 20(4), 490–495. <https://doi.org/10.1037/0894-4105.20.4.490>

Simpson, M. W., & Mak, M. (2019). The effect of transcranial direct current stimulation on upper limb motor performance in Parkinson's disease: a systematic review. *Journal of Neurology*, 267(0123456789), 1–10. <https://doi.org/10.1007/s00415-019-09385-y>

Smith, J. G., & McDowall, J. (2004). Impaired higher order implicit sequence learning on the verbal version of the serial reaction time task in patients with Parkinson's disease. *Neuropsychology*, 18(4), 679.

Smith, J., Siegert, R. J., McDowall, J., & Abernethy, D. (2001). Preserved implicit learning on both the serial reaction time task and artificial grammar in patients with Parkinson's disease. *Brain Cogn*, 45(3), 378–391. <https://doi.org/10.1006/brcg.2001.1286>

Soderstrom, N. C., & Bjork, R. A. (2015). Learning versus performance: An integrative review. *Perspectives on Psychological Science*, 10(2), 176–199.

Stephan, M. A., Meier, B., Zaugg, S. W., & Kaelin-Lang, A. (2011). Motor sequence learning performance in Parkinson's disease patients depends on the stage of disease. *Brain and Cognition*, 75(2), 135–140.

- Tombaugh, T. N., & McIntyre, N. J. (1992). The Mini-Mental State Examination: A Comprehensive Review. *Journal of the American Geriatrics Society*, 40(9), 922–935.
<https://doi.org/10.1111/j.1532-5415.1992.tb01992.x>
- Urry, K., Burns, N. R., & Baetu, I. (2015). Accuracy-based measures provide a better measure of sequence learning than reaction time-based measures. *Frontiers in Psychology*, 6, 1158.
- Vakil, E., Kahan, S., Huberman, M., & Osimani, A. (2000). Motor and non-motor sequence learning in patients with basal ganglia lesions: the case of serial reaction time (SRT). *Neuropsychologia*, 38(1), 1–10.
- Vandenbossche, J., Deroost, N., Soetens, E., Coomans, D., Spildooren, J., Vercruysse, S., Nieuwboer, A., & Kerckhofs, E. (2013). Impaired implicit sequence learning in parkinson's disease patients with freezing of gait. *Neuropsychology*, 27(1), 28–36. <https://doi.org/10.1037/a0031278>
- Vandenbossche, J., Deroost, N., Soetens, E., & Kerckhofs, E. (2009). Does implicit learning in non-demented Parkinson's disease depend on the level of cognitive functioning? *Brain Cogn*, 69(1), 194–199. <https://doi.org/10.1016/j.bandc.2008.07.005>
- Werheid, K., Ziessler, M., Nattkemper, D., & von Cramon, D. Y. (2003). Sequence learning in Parkinson's disease: the effect of spatial stimulus–response compatibility. *Brain and Cognition*, 52(2), 239–249.
- Westwater, H., McDowall, J., Siegert, R., Mossman, S., & Abernethy, D. (1998). Implicit learning in Parkinson's disease: Evidence from a verbal version of the serial reaction time task. *Journal of Clinical and Experimental Neuropsychology*, 20(3), 413–418.
<https://doi.org/10.1076/jcen.20.3.413.826>
- Wilkinson, L., Khan, Z., & Jahanshahi, M. (2009). The role of the basal ganglia and its cortical connections in sequence learning: Evidence from implicit and explicit sequence learning in Parkinson's disease. *Neuropsychologia*, 47(12), 2564–2573.
<https://doi.org/10.1016/j.neuropsychologia.2009.05.003>

- Williams-Gray, C. H., Foltynie, T., Brayne, C. E. G., Robbins, T. W., & Barker, R. A. (2007). Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. *Brain*, 130(7), 1787–1798.
- Wu, T, Wang, L., Hallett, M., Li, K., & Chan, P. (2010). Neural correlates of bimanual anti-phase and in-phase movements in Parkinson's disease. *Brain*, 133(Pt 8), 2394–2409.
<https://doi.org/10.1093/brain/awq151>
- Wu, Tao, & Hallett, M. (2013). The cerebellum in Parkinson's disease. *Brain*, 136(3), 696–709.
<https://doi.org/10.1093/brain/aws360>
- Wu, Tao, Wang, J., Wang, C., Hallett, M., Zang, Y., Wu, X., & Chan, P. (2012). Basal ganglia circuits changes in Parkinson's disease patients. *Neuroscience Letters*, 524(1), 55–59.
<https://doi.org/10.1016/j.neulet.2012.07.012>