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Implicit sequence learning in individuals with Parkinson's disease: The added value of using an ocular version of the serial reaction time (O-SRT) task

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ABSTRACT

Introduction: Though the majority of studies reported impaired sequence learning in individuals with Parkinson's disease (PD) tested with the Serial Reaction Time (SRT) task, findings are inconclusive. To elucidate this point, we used an eye tracker in an ocular SRT task version (O-SRT) that in addition to RT, enables extraction of two measures reflecting different cognitive processes, namely, *Correct Anticipation* (CA) and number of *Stucks*.
Methods: Individuals with PD ($n = 29$) and matched controls ($n = 31$) were tested with the O-SRT task, consisting of a repeated sequence of six blocks, then a block with an interference sequence followed by an original sequence block.
Results: Unlike controls, patients with PD did not improve in CA rate across learning trials, did not show an increase in RT when presented with the interference sequence, and showed a significantly higher rate of Stucks.
Conclusions: Low CA rate and high Stucks rate emerge as the cardinal deficits leading to impaired sequence learning following PD. These are viewed as reflecting difficulty in exploration for an efficient learning strategy. This study highlights the advantage in using the O-SRT task, which enables the generation of several informative measures of learning, allowing better characterization of the PD effect on sequence learning.

1. Introduction

The distinction between 'declarative' and 'procedural' memory systems introduced originally by Cohen and Squire (1980) is now well established. Declarative memory consists of facts (episodic memory) and events (semantic memory). This memory is typically expressed explicitly by recall or recognition tests. In contrast, procedural memory reflects the gradual acquisition of procedures and skills, following training and repetitions. The acquired procedural knowledge is expressed implicitly by improved performance as measured by accuracy and speed.

The critical role of the mid-temporal and diencephalic brain regions in declarative memory has been demonstrated in numerus neuroimaging studies and in amnesic patients with damage to these areas (for review, see Cohen et al., 1999; Davachi, 2006; Nichols, Kao, Verfaellie, & Gabrieli, 2006). Accumulating evidence indicates that brain regions subserving procedural memory are primarily the basal ganglia (BG) and the cerebellum (Saint-Cyr & Taylor, 1992). Neuroimaging studies have shown activation of the BG and cerebellum with various procedural learning tasks, such as probabilistic judgment (Poldrack et al., 2001). Further support for the involvement of the BG in procedural learning emerges from studies of patients with focal lesions to the BG (Vakil, Kahan, Huberman, & Osimani, 2000) and patients suffering from Parkinson's disease (PD), a disease that affects primarily the BG (Dubois & Pillon, 1996; Lang & Lozano, 1998). Individuals with PD have been reported to be impaired compared to matched controls on various tasks measuring procedural memory. For example, difficulties were detected in the acquisition of complex tracing skill (Frith, Bloxham, & Carpenter, 1986), solving the Tower of Toronto (Saint-Cyr, Taylor, & Lang, 1988), the Tower of Hanoi Puzzle (Daum et al., 1995; Vakil & Herishanu-Naaman, 1998) and a probabilistic learning task (weather prediction) (Knowlton, Mangels, & Squire, 1996).

One of the most frequently used tasks to assess procedural memory, or more specifically implicit sequence learning, is the serial reaction time (SRT) task (Nissen & Bullemer, 1987). In this task, participants see

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four squares horizontally presented on the screen, one square illuminated at a time. Participants are asked to respond with their index finger on horizontal keyboard numerical buttons, corresponding to the position of the illuminated square. Unbeknown to participants, they are presented with a repeated spatial sequence.

Several neuroimaging studies reported activation of the BG (the putamen and the caudate nucleus in particular) when performing the SRT task (Grafton, Hazeltine, & Ivry, 1995; Rauch et al., 1997; Schendan, Searl, Melrose, & Stern, 2003; Willingham, Salidis, & Gabrieli, 2002). See also a review (Packard & Knowlton, 2002) and a meta-analysis (Hardwick, Rottschy, Miall, & Eickhoff, 2013), confirming activation of the cortical-striatal circuitry in healthy participants while performing the SRT task.

The findings of studies using the SRT task to test patients with PD are not conclusive. The majority of studies reported impaired implicit sequence learning (e.g., Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Smith & McDowall, 2004; Stefanova, Kostic, Ziropadja, Markovic, & Ocic, 2000; Werheid, Ziessler, Nattkemper, & Von Cramon, 2003; Westwater, McDowall, Siegert, Mossman, & Abernethy, 1998). However, some studies reported either minor impairment or no impairment (e.g., Ferraro, Balota, & Connor, 1993; Pascual-Leone et al., 1993; Sommer, Grafman, Clark, & Hallett, 1999). Several meta-analyses were conducted in order to reach a more conclusive answer to the question whether PD affects implicit sequence learning measured with the SRT task. The meta-analysis conducted by Siegert, Taylor, Weatherall, and Abernethy (2006) was based on six studies and 67 individuals with PD tested on the SRT task. They used the cost (i.e., increase in RT) from the last block of the repeated sequence to the random sequence block. The increase in RT reflects sensitivity to the implicitly repeated sequence. Their conclusion was that individuals with PD have difficulties learning the implicit sequence. A more recent meta-analysis asking the same question, conducted on a larger sample ($n = 27$) of studies, including 505 patients with PD, reached the same conclusion that PD affects implicit sequence learning measured with the SRT task (Clark, Lum, & Ullman, 2014). It is important to note that researchers reached this conclusion despite the heterogeneity of results in the studies included in the meta-analysis. In their review of the literature, Ruitenberg, Duthoo, Santens, Notebaert, and Abrahamse (2015) also reached the conclusion that implicit sequence learning is impaired in patients with PD. Nevertheless, the fact that only 14 out of the 18 publications reviewed showed the impairment, further demonstrates the variability of these results.

Several attempts were made to explain the variability of the results. Some studies have pointed to variables related to the patients that mediate the effect of PD on implicit sequence learning (i.e., SRT task), such as severity or stage of the disease and effect of medication. Other studies pointed to variables associated with the SRT task, such as the sequence length and the amount of practice (for review, see Ruitenberg et al., 2015).

Smith and McDowall (2006) raised the very interesting question as to "whether SRT sequence learning in itself is a unitary phenomenon handled by a general-purpose sequence learning system which may (or may not) be affected by PD," (p. 276). In an attempt to address this question, the authors designed a verbal variation of the SRT task, which enables measurement of the spatial sequence, response (object) sequence and integrated spatial-response sequence. Their findings show that individuals with PD were able to acquire separately the spatial and object sequences, but not the integrated sequence. Therefore, their conclusion was that individuals with PD have difficulties in the integration of information from various dimensions, which leads to their difficulties in the SRT task.

The attempt in this study is to shed light on the effect of PD on implicit sequence learning as tested with the SRT task. The SRT task (Nissen & Bullemer, 1987) is frequently used to assess implicit sequence learning, which is a fundamental process in most skills we acquire including playing a musical instrument or learning to play tennis. One of the advantages of the SRT task is that it appears to be a very basic and simple task, compared to other tasks used in the literature to test procedural memory/skill learning. Unlike other tasks that are confounded with language (e.g., artificial grammar, mirror reading) or executive functions (e.g., Tower of Hanoi, Tower of Toronto) the SRT task only requires quick response to a square illuminated in red appearing on the screen.

Consistent with Smith and McDowall (2006) approach, we challenged the assumption that the SRT task reflects purely sequence learning. Accordingly, in the current study, we tested the possibility that part of the variability reported in the literature stemmed from the fact that the SRT task does not reflect a unitary process, and therefore it is not always clear what the exact effect of PD is. Possibly, this task consists of several cognitive sub-processes, learned simultaneously as a function of practice. To this end, we used an ocular version of the SRT task (O-SRT) that enables extraction of various measures that reflect different cognitive processes embedded in the task. The O-SRT task is an eye tracked variant of the SRT task, developed by Vakil, Bloch, and Cohen (2017). In addition to the typical RT measure used in the standard SRT test, this version of the task enables the generation of new measures. One of these measures is *Correct Anticipations* (CA). With the help of the eye tracker, we can evaluate whether the participant anticipated the subsequent target, by recording his/her eye movements during a 500 ms interval between targets (see Vakil et al., 2017). Another new measure is *Stucks*. Stucks describes the number of times the participant remains fixated on the previous target location, and then moves to the next location only when the new stimulus appears, rather than during the 500 ms delay between stimuli. This occular activation version of the O-SRT task is advantageous particularly for testing individuals with PD, because it does not require a manual response, which is deficient following PD. Furthermore, unlike in the standard SRT task, in this version of the task there is no need to learn the S-R mapping of the stimuli position on the screen and the corresponding manual response so that it is considered as a purer measure of implicit sequence learning (Vakil et al., 2017). Thus, with this version of the task, we are able to better characterize the differences between individuals with PD and matched health controls.

2. Method

2.1. Participants

Two groups participated in the present study: a group of healthy controls (CG) and a clinical group with PD. A total of 29 individuals with PD participated in the study, with ages ranging from 44 to 71 years ($M = 61.3$, $SD = 6.9$). The control group consisted of 31 individuals with normal or corrected vision. All control participants received a payment of 40 NIS (~10 US$). Their ages ranged from 41 to 72 years ($M = 59.6$, $SD = 8.2$). The groups' ages were not significantly different $t(58) = 0.87$, $p = 0.39$. The groups were further matched according to their years of education (PD: $M = 14.76.6$, $SD = 3.8$; Controls: $M = 14.55$, $SD = 2.4$, $t(58) = 0.26$, $p = 0.80$). Participants were recruited for the study from a population of patients receiving clinical treatment at the Movements Disorders Institute, Sheba Medical Center, Tel HaShomer (Israel). The diagnosis of idiopathic PD was made by a neurologist specializing in movement disorders, based on (a) the presence of at least two of the three cardinal symptoms (bradykinesia, rigidity and resting tremor) and (b) good response to chronic dopamine replacement therapy. Exclusion criteria included (a) diagnosis of dementia on the basis of clinical examination or a Mini-Mental State Examination score (MMSE) of 25 or less; (b) history or current evidence of other neurological and/or psychiatric disorders (including head trauma, substance abuse, and major depression); (c) use of active central nervous system therapies other than nocturnal sedatives and dopaminergic medications; (d) any prior neurosurgical intervention, including stereotactic procedures for PD. Twenty four participants of the PD group received medical treatment

with L-dopa formulations. Written informed consent was obtained from all participants. The study was approved as required by the Helsinki Committee at the Sheba Medical Center, Tel HaShomer, Israel.

2.2. Procedure

All participants completed the study procedures in a single testing session lasting approximately 30–40 min. First, participants were tested for possible cognitive decline with the MMSE. All participants who reached the cut off value of 26 points, were then administered the OA version of the O-SRT test, lasting approximately 20 min. The participants were then debriefed about the nature of the experiment.

2.2.1. Test material

2.2.1.1. Ocular activated O-SRT. The ocular activated version of the O-SRT task (Vakil et al., 2017) was used in this study. The task was programmed in E-Prime 2.0. Eye movements were recorded by the SMI iView 120 REDm Eye Tracker, at a sample rate of 120 Hz. Stimuli were presented on an LCD computer screen (Size 42 × 24 cm; resolution 1600 × 900 pixels). The recording device was installed beneath the screen. Participants were seated in front of the screen, approximately 60 cm away from it. Calibration was performed once at the beginning of the task session, using a standard 5-point grid for both eyes.

2.2.1.2. Stimuli. Stimuli consisted of five slides (see Fig. 1A), each with a resolution of 1400 × 900 pixels. Each stimulus included four white squares arranged in a diamond shape on a grey background. Four slides contained a black dot (indicating the target) in one of the four white squares. One slide, which was used to measure anticipation, contained only the four white squares, without a black dot in any of the squares. The size of each square was 6 × 6 cm and the diameter of the dot was 1.5 × 1.5 cm.

2.2.1.3. O-SRT procedure. A black dot (the target stimulus) appeared in one of four white squares arranged in a diamond shape (see Fig. 1A). Before each slide with a dot appeared on the screen, a blank slide with four empty squares was shown for 500 ms (i.e., the anticipation slide). Each block consisted of a 12-element sequence repeated nine times (see Fig. 1B). The sequence in each block began from a different element of the sequence, i.e., a different starting point. No first-order predictive information was provided in the sequence (i.e., each location is preceded by the same location only once). Each element in the sequence was matched with one of the four squares: 1, 2, 3, and 4 to correspond with down, left, right, and up, respectively. Two sequences were used in the O-SRT which were adopted from Gabriel et al. (2013): 'sequence A' (3-4-2-3-1-2-1-4-3-2-4-1; the original sequence) and 'sequence B' (3-4-1-2-4-3-1-4-2-1-3-2; the interference sequence). See Fig. 1B for an illustration of 'sequence A'.

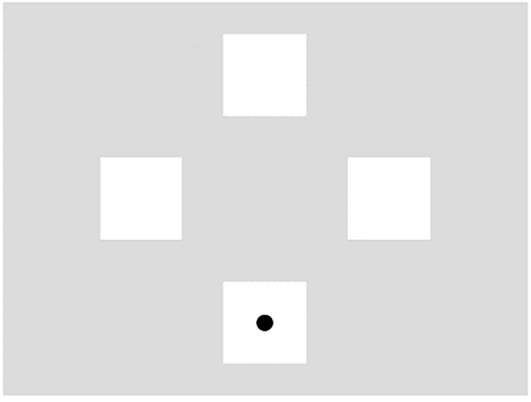

Fig. 1A. Illustration of the ocular serial reaction time (O-SRT) task. An example of a target slide. This slide was activated by 100 ms of fixation on the white square, or at the latest after 1000 ms if no fixation had occurred.

Participants were instructed to look as quickly as possible at the target dot when it appeared in one of the four squares arranged in a diamond shape. For the purpose of measuring anticipation of the subsequent target location, a blank slide was presented for 500 ms in between the target slides. Importantly, participants were not aware that a blank slide appeared, since it is perceived as a continuous flow from one to the next target slide. The target slides were oculomotor-activated (fixation of square with target for a minimum of 100 ms).

The O-SRT task was built from a total of eight blocks, divided into three phases. First, the *learning phase* – the presentation of six blocks (1–6) containing the original sequence A. Second, the *interference phase* – the presentation of one block with interference sequence B (block 7). Third, the *recovery from interference phase* – the presentation of one block with the original sequence A (block 8). After each block, a one-minute break was given before starting the next block. Participants received no prior information about the nature of the task (i.e., that the dots appear in a sequential order) nor the number of blocks.

2.3. Data analysis

Eye movement data was registered using IView (SensoMotoric Instruments, Teltow, Germany) and BeGaze™ (SensoMotoric Instruments, Teltow, Germany) was used to generate eye-tracking parameters. Three dependent measures were used: *Speed (RT to target), Percentage of Correct Anticipations (in the anticipation slide) and Percentage of Stucks*. Three phases of performance were analyzed separately: (1) *Learning*- block 1–6 in the learning session; (2) *Interference*- block 6 vs. block 7, and (3) *Recovery from Interference*- block 7 vs. block 8.

2.3.1. Reaction time

Median RT was calculated for each 12-item sequence (i.e., for each 12 target trials). Then, the mean of medians of RT per block (i.e., 9 sequences of 12-items each; 108 trials) was analyzed. Fig. 2 presents the mean of the medians of RT as a function of blocks 1 to 8 of the O-SRT for both groups.

2.3.2. Percentage of correct anticipations (Percentage CA)

Percentage CA was evaluated by tracking transition of the participant's gaze to the correct subsequent position during the blank slide inserted between the target slides presentation. We used the function "area of interest (AOI)" in the BeGaze program and enlarged the squares into triangles, so that four triangles cover the four squares and the center point of the screen (see Fig. 3).

During the 500 ms delay between stimuli, participants' gaze could focus on one of four possible AOIs: either at the correct location, on one of the two incorrect locations, or remain in the original location (Stuck). Our analysis showed that across all eight blocks, individuals with PD moved their gaze on average to the correct location in 25.8% of the trials, to the two incorrect locations combined in 27.0% of the trials, and in 47.2% of the trials their gaze remained in the same location. Compared to individuals with PD, controls' gaze moved to the correct location in 34.4% of the trials, in 34.0% of the trials to the two incorrect locations combined, and in 31.6% of the trials remained in the same location (Stuck).

The measure *Percentage of Correct Anticipations* (Percentage CA) included only the trials in which participants moved their gaze towards a different location. Trials in which participants' gaze shifted to more than one location (a negligible number, only 0.3% of trials) or remained at the same position (Stuck) were not included. Thus, the percentage of CAs analyzed and reported in Fig. 4 represents the ratio of number of trials in which participants' gaze moved towards the correct location, over the number of trials it moved to one of the two incorrect locations. Thus, percentage of CAs is independent of the percentage of Stucks. An

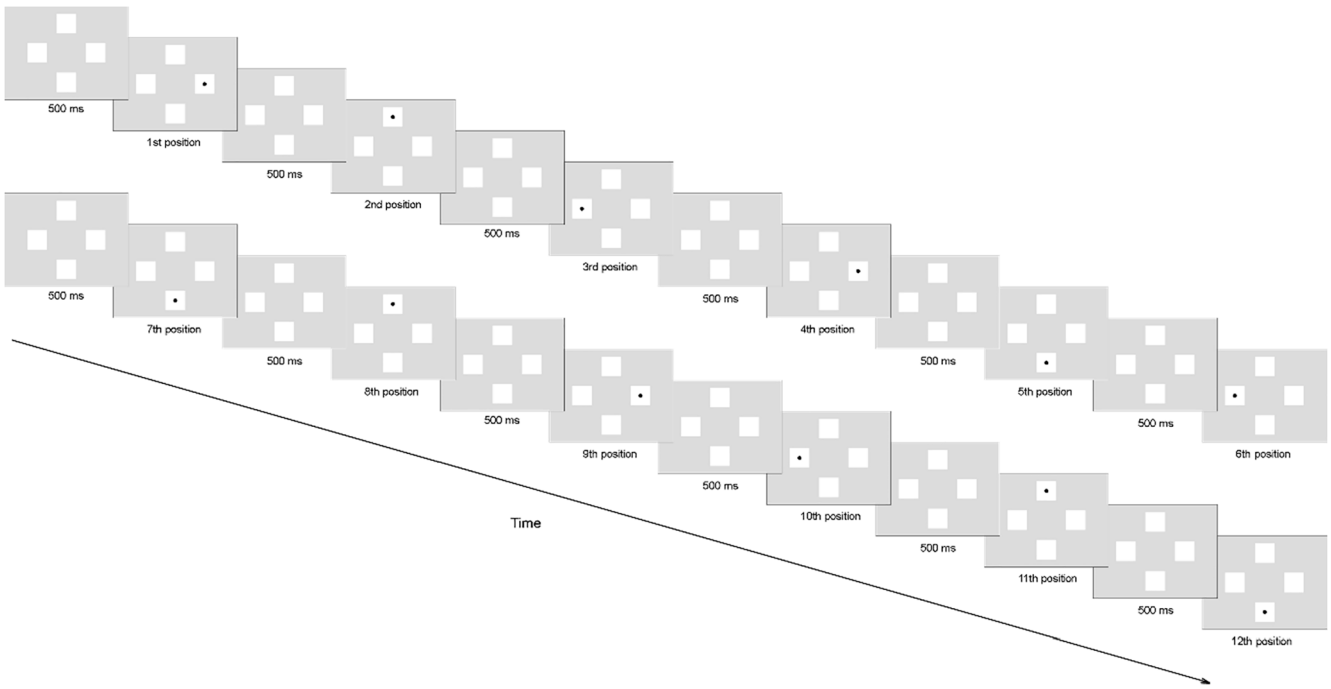

Fig. 1B. Illustration of one of the sequences used in the experimental design of the O-SRT task. A sequence consisting of 12 elements (i.e., positions) was repeated nine times per block. At the beginning and in between the target slides, an empty slide containing only the squares was presented for 500 ms in order to measure correct anticipations (CA) and Stucks. The same sequence (A) had been displayed in blocks 1–6, followed by an interference block 7 with a different sequence (B) and terminated by the recovery block 8 with the original sequence (A).

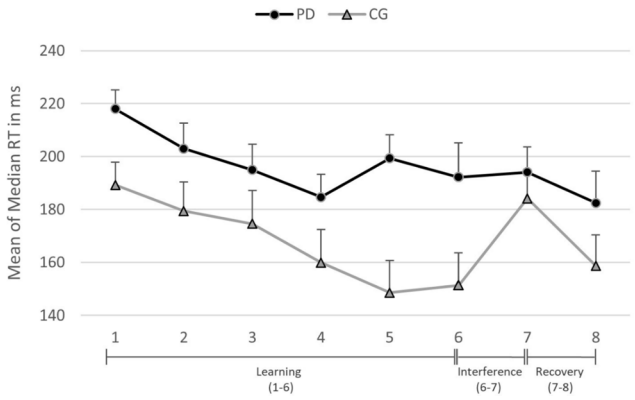

Fig. 2. The mean of the median reaction time of RT (SE) of the PD and control groups is displayed for blocks 1– 8. In the Learning phase, sequence A was presented from blocks 1 – 6. The 7th block contained the different sequence B (Interference phase), and finally in block 8 the original sequence A was presented again (Recovery from Interference phase).

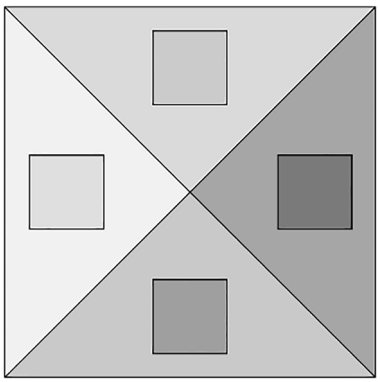

Fig. 3. The AOIs (areas of interest) used for calculating the correct anticipations. Each triangle was considered the AOI for the square that was positioned inside of it.

anticipation score of "1″ was set for the slides in which there was at least one fixation on the correct location only (where the next target was going to appear), and a "0″ score for fixations on one of the incorrect locations. Then, the number of correct anticipations per sequence (average anticipation score range: 0–12) was counted and averaged for nine sequences per block. This established the Percentage correct anticipations (percentage CA) score for each block for all participants. Fig. 4 presents the Percentage CA (as a function of blocks 1 to 8 of the O-SRT for both groups.

2.3.3. Percentage of Stucks

This measure included only the trials in which the participant's gaze remained at the previous location. The Percentage of Stucks was computed out of the total stuck trials relative to the total number of trials per block. Fig. 5 presents the percentage of Stucks (as a function of blocks 1 to 8 of the O-SRT for both groups.

These three measures (i.e., RT, Percentage CA and Percentage Stuck) were analyzed for each one of the phases of the task (i.e., Learning, Interference, and Recovery from interference).

Learning: Mixed-design analysis of variance (ANOVA; 2 × 6) was used to analyze the effects of the between-subjects condition factor of Group (PD and Controls) and the within-subjects factor of Learning (blocks 1–6)

Interference: Mixed-design ANOVA (2 × 2) was used to explore the effect of the between-subjects condition factor of Group (PD and Controls) and the within-subjects factor of Interference (block 6 vs. block 7).

Recovery from Interference: Mixed-design ANOVA (2 × 2) was used to explore the effect of the between-subjects condition factor of Group (PD and Controls) and the within-subjects factor of Recovery from Interference (block 7 vs. block 8).

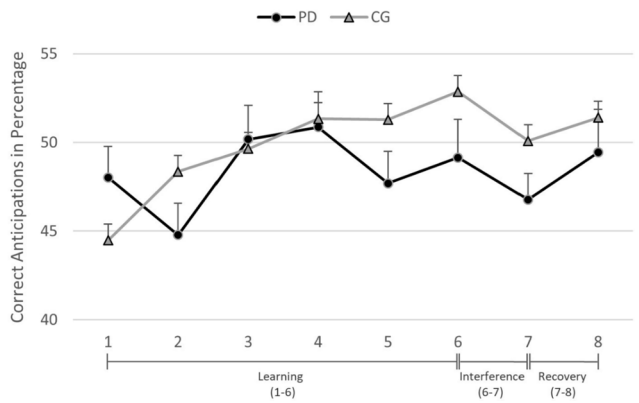

Fig. 4. The mean number (SE) of correct anticipations (CA) of the ocular serial reaction time (O-SRT) task for the PD and the control groups is displayed for blocks 1 – 8. In the Learning phase, sequence A was presented from blocks 1 – 6. The 7th block contained the different sequence B (Interference phase), and finally in block 8 the original sequence A was presented again (Recovery from Interference phase).

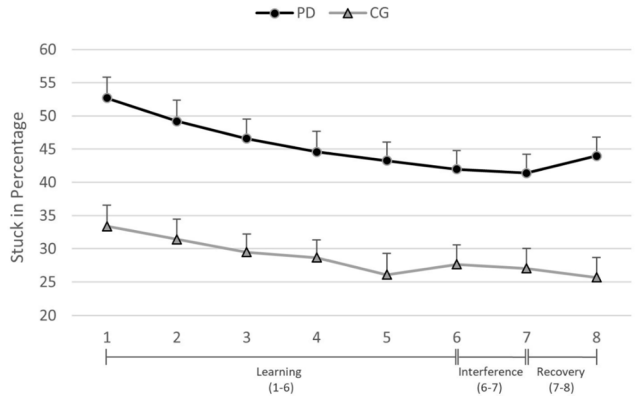

Fig. 5. The mean of the percent of number of Stucks (SE) of the PD and control groups is displayed for blocks 1– 8. In the Learning phase, sequence A was presented from blocks 1 – 6. The 7th block contained the different sequence B (Interference phase) and finally in block 8 the original sequence A was presented again (Recovery from Interference phase).

3. Results

3.1. Reaction time

Learning: A mixed ANOVA with a Greenhouse-Geisser correction revealed a significant Learning effect, reduction in RT over blocks 1–6, $F(3.8, 220.39) = 6.51$, $p < .001$, $\eta_p^2 = 0.10$, see Fig. 2. The main effect of Group reached significance as well, $F(1, 58) = 6.75$, $p < .05$, $\eta_p^2 = 0.10$. Group by Learning interaction was not significant, $F(3.8, 220.39) = 1.40$, $p = .24$, $\eta_p^2 = 0.02$. These results indicate that both groups significantly reduced the RTs during the Learning phase. Additionally, the PD group performed generally slower than the control group.

Interference: Interference effect, $F(1, 58) = 5.34$, $p < .05$, $\eta_p^2 = 0.08$, and interaction of Group and Interference, $F(1, 58) = 4.26$, $p < .05$, $\eta_p^2 = 0.07$, both reached significance. The Group effect was marginally significant, $F(1, 58) = 3.07$, $p = .09$, $\eta_p^2 = 0.05$. Follow up analyses revealed that only the control group showed a significant interference effect (PD: $F(1, 28) = 0.034$, $p = .86$, $\eta_p^2 = 0.001$, controls: $F(1, 30) = 8.74$, $p < .01$, $\eta_p^2 = 0.23$). These results indicate that interference only affected the control group, which demonstrated higher RTs when a different sequence was presented (see Fig. 2).

Recovery from Interference: Recovery main effect, reached significance, $F(1, 58) = 8.96$, $p < .01$, $\eta_p^2 = 0.13$. Group by Recovery from Interference interaction, $F(1, 58) = 1.24$, $p = .27$, $\eta_p^2 = 0.02$ as well as Group main effect, $F(1, 58) = 1.34$, $p = .25$, $\eta_p^2 = 0.02$, did not reach significance. According to these results, both groups recovered in a similar way from the interference sequence.

3.2. Percentage of correct anticipations (CA)

Learning: Learning main effect, $F(5, 290) = 4.88$, $p < .001$, $\eta_p^2 = 0.08$, as well as Group by Learning interaction, $F(5, 290) = 2.34$, , $p < .05$, $\eta_p^2 = 0.04$, were both significant. Main effect for Group, $F(1, 58) = 0.54$, $p = .47$, $\eta_p^2 = 0.009$, did not reach significance (see Fig. 4). To detect the source of the interaction, we performed a follow up analysis (i.e., separate Repeated Measures ANOVA; Sphericity was assumed for the control but not the PD group; therefore, we used a Greenhouse-Geisser correction for the latter) which demonstrated that the Learning effect was significant only in the control, $F(5, 150) = 6.12$, , $p < .001$, $\eta_p^2 = 0.17$, but not in the PD group, $F(3.45, 96.72) = 1.99$, , $p = .11$, $\eta_p^2 = 0.07$.

Interference: None of the effects reached significance: Interference main effect, $F(1, 58) = 2.68$, $p = .11$, $\eta_p^2 = 0.04$, Group by Interference $F(1, 58) = 0.02$, $p = .90$, $\eta_p^2 = 0.001$ and Group main effect, $F(1, 58) = 3.57$, $p = .06$, $\eta_p^2 = 0.06$. These results imply that both groups were not significantly affected by the interference sequence.

Recovery from Interference: None of the effects reached significance: Recovery from Interference main effect, $F(1, 58) = 1.75$, $p = .19$, $\eta_p^2 = 0.03$, Group by Recovery from Interference $F(1, 58) = 0.20$, $p = .66$, $\eta_p^2 = 0.003$ and Group main effect, $F(1, 58) = 1.62$, $p = .21$, $\eta_p^2 = 0.03$. These results demonstrate that both groups did not significantly recover from the interference sequence.

3.3. Percentage of Stucks

Learning: A mixed ANOVA with a Greenhouse-Geisser correction revealed a significant Learning main effect, $F(3.8, 220.8) = 9.69$, $p < .001$, $\eta_p^2 = 0.14$. Furthermore, the main effect for Group, $F(1, 58) = 20.25$, $p < .001$, $\eta_p^2 = 0.26$ was also significant. Group by Learning interaction did not reach significance, $F(3.8, 220.8) = 0.65$, $p = .62$, $\eta_p^2 = 0.01$. Overall, these results indicate that as the session progressed, both groups showed a similar decrease in Percentage Stuck. However, the PD group had a significantly higher percentage of Stucks compared to the controls (see Fig. 5).

Interference: Interference main effect, $F(1, 58) = 0.19$, $p = .67$, $\eta_p^2 = 0.003$, as well as the Group by Interference interaction $F(1, 58) = 0.001$, $p = .99$, $\eta_p^2 = 0.001$, did not reach significance. Group main effect was significant, $F(1, 58) = 13.60$, $p < .001$, $\eta_p^2 = 0.19$. These results suggest that the Stucks were not affected by the interference sequence in both groups and that PD generally had a higher amount of Percentage of Stucks in comparison to the controls.

Recovery from Interference: Recovery from Interference main effect, $F(1, 58) = 0.20$, $p = .66$, $\eta_p^2 = 0.003$, as well as the Group by Recovery from Interference interaction $F(1, 58) = 2.01$, $p = .16$, $\eta_p^2 = 0.03$, did not reach significance. Group main effect was significant, $F(1, 58) = 17.37$, $p < .001$, $\eta_p^2 = 0.23$. These results suggest that both groups did not demonstrate a recovery from the interference sequence. Furthermore, the PD group expressed a higher amount of Percentage of Stucks compared to the controls.

3.4. Correlation analyses

In order to analyze the correlations between the three sequence learning measures (i.e., RT, percentage of CA, percentage of Stucks) we calculated the average of the six learning blocks for each one of these measures. Pearson product moment correlations were conducted separately for each group. The correlation between RT and percentage CA reached significance only for the control group $r(29) = -0.551$, $p < 0.01$, but not for the patients with PD, $r(27) = -0.277$, $p = 0.15$. For both groups a significant positive correlation was found between RT and

Stucks, $r(27) = 0.515$, $p < 0.01$; $r(29) = 0.828$, $p < 0.001$, for the PD group and control group, respectively. The correlation between CA measure and the Stucks measure was significantly negative for the control group, $r(29) = -0.500$, $p < 0.01$, but was not significant for the group with PD, $r(27) = -0.076$, $p = 0.70$).

4. Discussion

Although the literature on the effect of PD on performance on the SRT task is not conclusive, the majority of studies report impaired performance on the SRT task of patients with PD (for review, see Ruitenberg et al., 2015). This conclusion was confirmed by two meta-analyses that addressed this issue (Clark et al., 2014; Siegert et al., 2006). The inconsistency was attributed either to patients' characteristics such as severity of the disease or the medication, or to task characteristics such as sequence length and amount of training (for review, see Ruitenberg et al., 2015).

Following Smith and McDowall (2006), we challenged the assumption that the SRT task is a simple and uniform task. For that reason, in the current study we tested the possibility that the variability reported in the literature stemmed partially from the fact that the SRT task does not reflect a unitary process, and therefore it is not always clear what the exact effect of PD is. Hence, we used the O-SRT task, which enables generation of several learning measures reflecting different cognitive processes embedded in the implicit sequence learning process. Our assertion is that integration of the three learning measures generated from the O-SRT task (i.e., RT, CA & Stucks) would give us a more comprehensive understanding in implicit sequence learning of the difference between individuals with PD and healthy controls.

When looking at the RT measure the picture emerging is that the patient group are overall slower in responding to the stimuli. Interestingly, the learning rate over the six learning trials did not differ significantly. However, as can be seen in Fig. 2, the gap between the groups increases as training progresses (blocks 5 and 6), which might indicate that this difference would have increased further with more extensive training. The two meta-analyses addressing the effect of PD on SRT task performance (Clark et al., 2014; Siegert et al., 2006) used the shift to a random or different sequence from the repeated learned sequence as the most sensitive mesure of sequence learning. Consistent with their conclusion, here, too, unlike the healthy controls who showed cost (increased RT) in the interference block compared to the last learning block (6th vs. 7th block), the PD group did not show such an effect (see Fig. 1).

Analysis of the percentage CA measure indicates that unlike the healthy control group that showed significant increase in p percentage CA across the six learning blocks, patients with PD did not show such an improvement. Interestingly, the percentage CA was not reduced significantly for both groups when the different sequence was introduced. The fact that the control group did not show this reduction in percentage CA is surprising in light of the findings of Vakil et al. (2017) that showed a significant decrease. One possible explanation is that in Vakil et al.'s original paper the group was younger ($M = 23.8$ years, range 18–32 years) than the healthy control group in the present study ($M = 59.6$ years, range 41–72 years). Further research is required in order to determine the effect of aging on the O-SRT task.

The main findings of the analyses of the Stuck measure are as follows: First, individuals with PD made overall significantly more Stucks along all the phases of the task. Second, the learning effect was significant and similar for both groups. Third, there was no interference effect, nor did it interact with group. As can be seen in Fig. 5, for both groups performance did not change from block 6 to 7. The question we would like to address first is what is the explanation for the reduction of the number of Stucks through training? Or in other words, what is learned? One possible interpretation is that participants remained focused in the previous location as their default response, but they would attempt to move to the next position only when beginning to feel secure in knowing the subsequent appearing target location. So as training progresses, participants gradually learn the sequence of the spatial position and do not remain in the previous location (i.e., Stuck), but make moves toward the direction they anticipate the next stimulus will appear. The fact that there is no increase in the number of Stucks when the new sequence is presented in block 7 argues against this interpretation. Now the participant must have noticed that predictions that should have led them to increase the percent of Stucks until the new sequence is learned, are incorrect. The alternative interpretation is that what is actually learned is one of the statistical charecteristics of the sequence, that the target location never remains the same in a subsequent trial. The new sequence introduced in block 7 obeys the same statistical characteristics as the trained sequence. Therefore, the percentage of Stucks does not increase when the interference sequence is presented.

The intercorrelations between RT, CA and Stucks measures give us further insight into the interaction between these measures, and shed light on the unique method of implicit sequence learning in each group. The positive relation of average RT and average percentage Stuck which was observerd in both groups is explained by a feature of the O-SRT task. Namely, RT will be longer if a participant is stuck in the previous position, and starts to move towards the next position only when the target stimuli appears, compared to trials when a participant already moves towards the target during the 500 ms delay before it appears.

The correlations in which the control, but not the PD group, showed significant correlations are very informative, namely, the positive correlation between average RT and average percentage CA and the negative correlation between average percentage CA and average percentage Stucks. The positive correlation found in the control group between the average percentage CAs and average RT is expected. That is because several studies have assumed that improved RT in the SRT task is the result of improved correct anticipations of the next target location (Cleeremans & McClelland, 1991; Marcus, Karatekin, & Markiewicz, 2006). It is important to note that this has been an assumption ever since the standard SRT task was developed. However, unlike the O-SRT task used in this study, anticipations are not directly measurable in the standard SRT task. The negative correlation between average percentage CA and average percentage Stucks suggests that the lower the percentage of Stucks, the higher the CA rate. Following the interpretation presented earlier, the low percentage of Stucks reflects statistical learning of one of the characteristics of the sequence, which is that the target never remains in the same location, and this insight leads to increased CAs. Thus, for the healthy control group the three expressions of learning are interrelated. The repeated practice of the sequence leads simultaneously to increased CAs and a decreased number of Stucks (which are associated with each other, as both are expressions of the sequence learning), both of which lead to faster responses expressed in decreased RT through the learning blocks. For the patients with PD, it seems that only the decrease in number of Stucks affects improved RT. As explained earlier the decrease in number of Stucks (although still at a significantly higher rate than in controls) reflects learning of one of the characteristics of the sequence that definitely is expressed in faster RT, but does not reflect learning of the sequence itself. This is consistent with the findings that the patient group showed learning in the first six blocks, but RT was not affected when the sequence was changed, an indication that they had not really learned the sequence itself. In this group, unlike controls, there is no indication of learning of the CAs, and CA is not correlated either with the number of Stucks or with RT.

In summary, impairment of CA rates and high rates of Stucks emerge as the cardinal deficits leading to impaired implicit sequence learning following PD. This is consistent with the conclusion reached by several researchers that patients with PD have difficulties in attaining and mobilizing effective task strategy in the process of procedural learning (Frith et al., 1986; Soliveri, Brown, Jahanshahi, Caraceni, & Marsden, 1997). In a previous study using the Tower of Hanoi puzzle as a cognitive skill-learning task, we reached a similar conclusion that patients with PD have a problem in exploring for optimal task solution (Vakil,

Hassin-Baer, & Karni, 2014). Similarly, animal studies conducted by Doya (1999) and Parush, Tishby, and Bergman (2011) have demonstrated the effect of dopamine depletion on task solution explorations. Thus, low CA and high Stucks rates observed in individuals with PD are viewed as reflecting a problem in exploration for an efficient strategy, rather than a specific deficit in implicit sequence learning. This study highlights the advantage of using the O-SRT task over the standard SRT task. In this version of the task, the use of eye tracking enables the extraction of several measures reflecting different sub cognitive processes involved in the seemingly unitary SRT task. And as demonstrated in this study, these additional measures (i.e., CA & Stucks) are more informative than the typical RT measure, regarding the effect of PD on implicit sequence learning.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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