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What neurological diseases tell us about procedural perceptual-motor learning? A systematic review of the literature

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Abstract

Introduction Procedural perceptual-motor learning of sequences (PPMLS) provides perceptual-motor skills in many activities of daily living. Based on behavioral and neuroimaging results, theoretical models of PPMLS postulate that the cortico-striatal loop, the cortico-cerebellar loop and the hippocampus are specifically involved in the early stage of PPMLS while the cortico-striatal loop would be specifically involved in the late stage of PPMLS. Hence, current models predict that the early stage of PPMLS should be impaired in Parkinson's disease (PD: lesion of the cortico-striatal loop), in cerebellar disease (CD: lesion of the cortico-cerebellar loop) and in Alzheimer's disease (AD: lesion of the hippocampus), whereas the late stage of PPMLS should be specifically impaired in PD.

Objective The aim of the study is (1) to draw a complete picture of experimental results on PPMLS in PD, CD and AD (2)

to understand heterogeneity of results as regard to participant and task characteristics.

Method This review is based on the guideline proposed by the PRISMA statement.

Results Our review reveals (1) that the experimental results clarify the theoretical models and (2) that the impairment of PPMLS depends on both the personal characteristics of the participants and the characteristics of the task to-be-learned rather than on the disease itself.

Conclusion Our results highlight that these characteristics should be more carefully considered to understand the heterogeneity of results across studies on PPMLS and the effects of rehabilitation programs.

Keywords Procedural memory · Serial reaction time task (SRTT) · Alzheimer's disease · Parkinson's disease · Cerebellar lesions

Introduction

Dissociation of procedural perceptual-motor learning from other systems of learning and memory

Procedural perceptual-motor learning refers to the acquisition of perceptual-motor skills (encoding, storage and retrieval) [1]. It is acquired incrementally with practice, often implicitly, through repeated exposures to stimuli [2]. This learning is particularly relevant in rehabilitation of patients with neurodegenerative diseases or lesions when the aim is to (re-)learn perceptual-motor skills in order to maintain daily life activities (driving, cycling, tying shoes, making coffee, reading, writing, etc.). Procedural perceptual-motor learning is dissociated from declarative learning. As initially revealed in studies on the famous patient H. M. [3], amnesic patients with medial temporal lobe lesions, including the hippocampus, may show severe amnesia (i.e., inability to

remember events) but intact acquisition and retention of perceptual-motor skill (e.g., tracking, mirror tracing) [4]. The opposite dissociation is found in patients with neurodegenerative diseases of striatum (as in Parkinson's disease) who are able to learn declarative knowledge but unable to learn procedural skills [5]. These findings suggested a dual functional dissociation between procedural memory containing rule-based information ("knowing how") and declarative memory containing data-based information ("knowing that") [6].

Procedural perceptual-motor learning is implicit, persistent, and robust

Unlike declarative memory, procedural perceptual-motor learning is considered to be an implicit acquisition because skills are acquired without conscious awareness [7, 8]. Procedural perceptual-motor learning is also considered a robust system for storing stable and persistent skills. Procedural perceptual-motor learning is characterized by a progressive improvement in performance (speed and/or accuracy) that evolves slowly with repeated practice [9–11]. Learned motor skills can be recalled after several months or even years of no practice [12–14]. Also, procedural perceptual-motor learning is supposed to be relatively preserved in normal aging [15, 16] and in diseases with degenerative lesions involving the hippocampal structure (such as Alzheimer's disease) [17, 18]. As an example, brain-injured patients with medial temporal lobe damage present a persistent retention of procedural skills in real-world activities 2 months after initial practice [19].

Procedural perceptual-motor learning of sequences (PPMLS) in healthy population

Based on the neural correlates, procedural perceptual-motor learning is divided in two subsystems: the first corresponds to procedural perceptual-motor learning of sequences (PPMLS) and the second corresponds to the perceptual-motor adaptation, which is the compensation of movements in the face of environmental changes [5]. Procedural perceptual-motor learning of sequences (PPMLS) has been extensively studied using the serial reaction time task (SRTT). Participants sit in front of a screen with four visual stimuli (typically squares aligned horizontally) and a keyboard with four keys. The position of each key corresponds to the position of one of the four stimuli of the screen (spatial correspondence). Participants are asked to press a key corresponding to the stimulus position as quickly and accurately as possible [20]. Unbeknownst to the participant, visual cues play a repetitive sequence of positions. Results typically show that response times and errors decrease during the sequential trials. Thus, participants learn the perceptual-motor sequence through repeated practice. In other words, they learn to predict the occurrence of each next position. When a random block of stimuli is introduced (visual cues no longer play a repetitive pattern of positions), response times and errors increase significantly [20]. Overall, the decrease in RTs and/or errors with practice provides evidence of *general learning*. In contrast, the increase in RTs and/or errors when the random block of stimuli is introduced suggests a *specific-sequence learning* of the perceptual-motor sequence [21]. Skill acquired with the SRTT can be retained for periods of up to 1 year, specific-sequence learning especially [22].

The model of Doyon and Benali [23] supports that PPMLS subsystem is functionally and structurally dissociated from the perceptual-motor adaptation subsystem that allows compensations of movements for environmental changes. These two subsystems are supported by two underlying neural networks that specialize as learning progresses [9, 23]. More precisely, PPMLS would imply more and more the cortico-striatal loop, whereas the perceptual-motor adaptation would imply more and more the cortico-cerebellar loop [5].

Time course of PPMLS

Based on studies with monkeys or humans, the model of Hikosaka [24] suggests that PPMLS occurs at two levels: the first level allows perceptual learning (the sequence of locations of the stimulus), and the second level allows motor learning (the sequence of fingers tapping on the keys). Perceptual learning is assumed to develop rapidly, independently of effectors and in an explicit form, and to be dominant in the early stage. Motor learning is

assumed to develop more slowly and implicitly, integrating and representing the dynamic aspects of movements in order to optimize the execution of the sequence by the specific effectors; it is the dominant representation in later stage [24]. In healthy participants, motor learning and perceptual learning appear to follow different temporal courses of consolidation. Hallgató [25] used an adapted SRTT to determine whether consolidation had identical or different effects on the perceptual and motor components of skill acquisition. All participants performed a sequence learning task in the first session. In the second session, half of the participants received a new sequence with the same motor information but different perceptual information than in the first session (motor condition). The other half of the participants received the same perceptual information but different motor information than in the first session (perceptual condition). The motor condition induced a larger sequence learning effect than the perceptual condition [25]. In accordance with the model of Hikosaka [24], perceptual and motor learning can be considered as independent learning systems [26]. At a neural level, perceptual learning would be supported by a network involving the anterior striatum and cerebellum (early stage), while motor learning would be supported by a network involving the posterior striatum (late stage) [27]. This hypothesis has been reinforced by previous empirical investigations showing that activations of the most anterior parts of the striatum seem to be more important in the early stage of sequential association learning, while the posterior parts play a more important role in the later stage (see meta-analysis [28]). At a neural level, during the early learning stage (fast learning), both PPMLS and perceptual-motor adaptation are supposed to recruit similar cerebral structures (striatum, cerebellum, hippocampus, motor cortical regions). On the contrary, during the later stage (slow learning), differential contributions of the cortico-striatal and cortico-cerebellar systems occur. More precisely, the cortico-striatal, cortico-cerebellar, and hippocampal systems are crucial for the construction of the motor memory trace in the early stage, which will then be consolidated and maintained over time within a more specialized subsystem, the cortico-striatal system Fig. 1A.

In the same way as Hikosaka's model [24], Doyon and Benali's model [23] describes several stages of perceptual-motor learning [9]. Firstly, the *fast learning* stage is characterized by fast and considerable improvement in performance with practice (early stage). Secondly, the *slow learning* stage corresponds to further incremental gains in performance that can be observed over several practice sessions (late stage). Thirdly, the *consolidation* occurs during the interval between practice sessions. It corresponds to spontaneous increases in performance that can be observed after a latent period of 4 to 6 h, according to the authors, without additional practice after the first training session, or in which no interference from a competing task can be observed. The consolidation process is the stabilization of the representation in memory, leading to an increased resistance to interference when another skill is practiced during this delay [29–31]. Fourth, the *automatic stage* in which the skill requires minimal cognitive resources and is resistant to interference and the effects of time. Finally, a *retention* stage in which the motor skill can be executed after long delays without practice [23]. Even if it is difficult to separate each of these stages during learning, Janacsek [28] proposed that the first day of SRTT training can be considered as the early stage of sequence learning and that later stage occurs in a second day.

Predictions of the current models and neuroimaging studies about the deficits in PPMLS in lesions of the striatum, the hippocampus, and the cerebellum

A summary of the models of Doyon and Benali [23] and Hikosaka [24] is illustrated in Fig. 1A. According to both models, the early stage of PPMLS should be specifically impaired in diseases involving a lesion of the striato-cortical loop (i.e., Parkinson's disease), a lesion of the cortico-cerebellar loop (i.e., cerebellar disease) or a lesion of the hippocampus (i.e., Alzheimer's disease). In contrast, the late stage of PPMLS should be specifically impaired in lesions of the striato-cortical loop (i.e., Parkinson's disease). However, the role of the cerebellum in the early stage of learning is the subject of intense debate [28, 32].

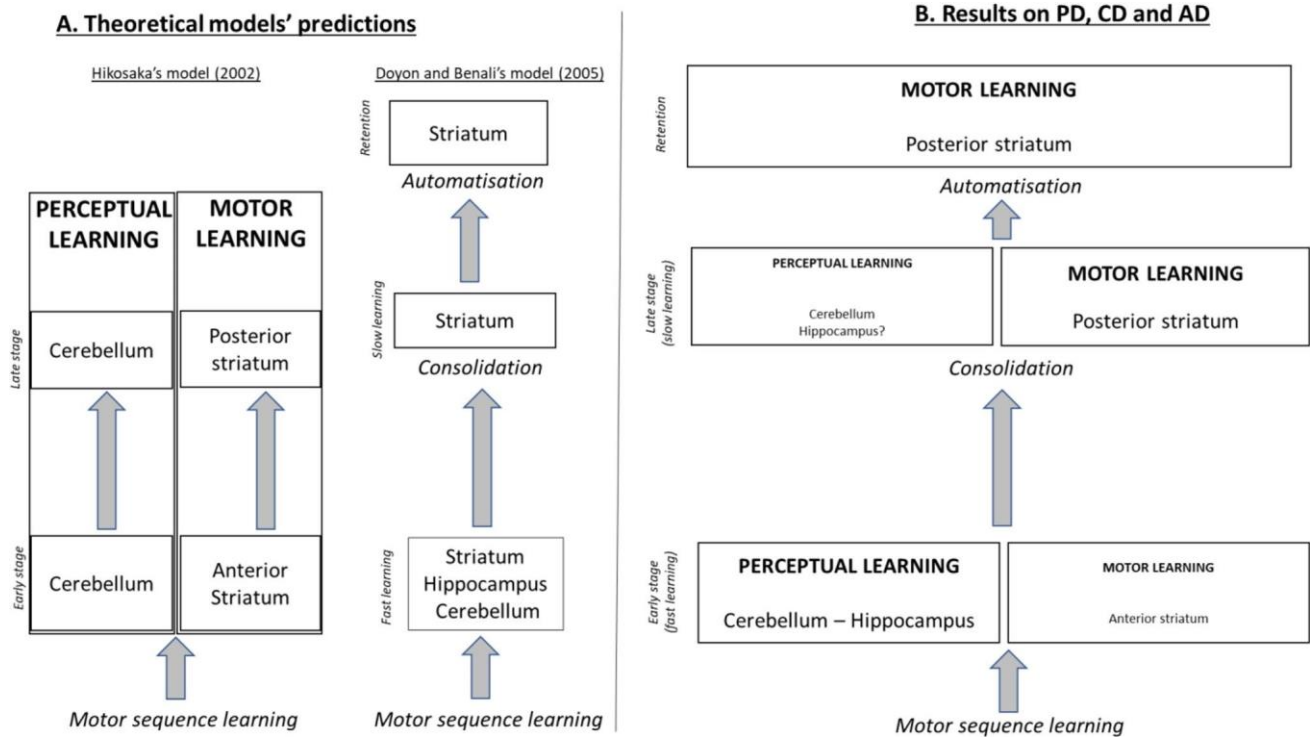


Fig. 1 Theoretical model's predictions (A) and results (B) on PD, CD, and AD (PD = Parkinson's disease, CD = cerebellar disease, AD = Alzheimer's disease)

A substantial number of studies have used the SRTT to examine how PPMLS is impaired in the Parkinson's disease (PD). However, research is sparse on PPMLS in the Alzheimer's disease (AD) and in cerebellar patients (CD). Four meta-analyses [33–36] and one systematic review [37] have presented the state of research on PPMLS in PD and AD, but separately and without considering learning stages. The most comprehensive meta-analysis in PD was conducted 10 years ago and summarized 27 researches using SRTT and indicated a significant deterioration of PPMLS in PD compared to controls ($p < 0.001$) [33]. The effect size was 0.531 (95% CI [0.322, 0.740]) and suggested a moderate impairment of PPMLS in PD. The second meta-analysis provided the same conclusion given it used the first meta-analysis [33] but extended to neurodevelopmental disorders [34]. A third meta-analysis included six studies, including 67 patients with PD [36]. A significant impairment of PPMLS was found for PD compared to controls, with a standardized mean difference of 0.73 (95% CI [0.38, 1.07]). The last meta-analysis included only studies using a final block of random practice trials, hence focusing on the late stage of PPMLS [35]. Fifteen articles met their final criteria and assessed 299 individuals with PD for a significant effect size of 0.83. All in all, meta-analyses in patients with PD concluded that PPMLS was moderately impaired in PD, suggesting an impaired late stage of PPMLS in PD. The systematic review conducted on PPMLS in patients with AD selected only 4 studies and found relatively intact PPMLS although under certain conditions PPMLS seems to be impacted in AD [37]. The problematic of early vs late learning was not discussed. We did not find any meta-analyses or reviews focusing on the effect of CD lesions on PPMLS. To sum up, the previous meta-analyses conducted on PPMLS only focused on PD and reported considerable heterogeneity in outcomes and effect sizes. It is now necessary to identify the source of this heterogeneity, i.e., the factors that may or may not alter PPMLS.

Aim of the current systematic review

Today, PPMLS is explained by two separated theoretical neuroscientific models [23, 24]. Our systematic review aims to offer a complete and exhaustive picture of the current findings about PPMLS by providing an integrated

model based on the results of scientific literature. Hence, for the first time, our systematic review of the literature challenges the predictions of current models of PPMLS by analyzing exhaustively the literature on PPMLS in PD, AD, and CD in early and later learning stage. One approach aims to clarify the functional neuroanatomy of PPMLS. In addition, to consider the heterogeneity of the results, this systematic review also aims to identify the factors modulating PPMLS in the three neurological diseases.

Methods

General methodology (PICOS)

This review is based on the PRISMA guideline and its item checklist [38]. To define the review question and develop criteria for inclusion of studies, we relied on a structured approach to question formulation, using five elements [39]. This approach is commonly known by the acronym “PICOS,” where each letter refers to a component: the patient population or the disease (P) the interventions or exposure (I), the comparator group (C), the outcome or endpoint (O), and the study design (S) (we do not use this last characteristic here). Here is the equation entered in PubMed: (“Diseases

Category”[MeSH] OR “disease” OR “pathology” OR “pathology”[MeSH]) AND (“learning”[MeSH] OR “learning” OR “memory”[MeSH] OR “memory”) AND (“Neurodegenerative diseases”[MeSH] OR “Neurodegenerative diseases”[All Fields] OR “Cerebellar Diseases”[MeSH] OR “cerebellar”) AND (“procedural” OR “Serial Reaction Time” OR “SRTT” OR “motor sequence”).

Here is the equation entered in ScienceDirect: (“degenerative disease” OR “cerebellar disease”) AND (“procedural learning” OR “procedural memory” OR “Serial Reaction Time” OR “SRTT” OR “motor sequence”) by checking “review” and “research articles.”

Study selection

Electronic databases of published literature were searched using ScienceDirect and PubMed. This literature was supplemented by previous meta-analyses and reviews. Additional articles of interest were obtained through literature reviews and based on the authors’ knowledge. The search was conducted in English and included research papers and pilot studies. The following key terms were searched: learning, memory, procedural, neurodegenerative diseases, cerebellar lesions, serial reaction time, SRTT, and motor sequence.

The search strategy was executed in January 25, 2023, and no limit has been set for publication years. We have not attempted to identify studies of “gray” literature, such as conference proceedings or research published in theses, and we include only articles published in English. However, by limiting the systematic review to peer-reviewed journals, we have based our conclusions on the highest quality studies possible. Reference lists were manually scanned by two independent assessors (EM and CSB), who selected titles and abstracts. Studies were included after agreement of the authors (EM and CSB), and discrepancies were resolved by a third researcher (JT).

The collection and management of the studies were carried out with Zotero 5.0.96 (2021).

Inclusion and exclusion criteria

Articles were only included if they met eligibility criteria based on Population-Intervention-Comparison-Outcome (PICO) components [39]:

- Participants: Studies of adults with AD, PD, or CD were included. Studies with participants who presented another neurodegenerative disease (Lewy bodies disease, Huntington’s disease, multiple sclerosis, etc.) were not included.
- Intervention: Studies were included if they reported behavioral data that related to processes or mechanisms

of motor procedural learning. Studies about verbal procedural memory, declarative memory, or working memory were not included.

- Comparison: Studies were not included if they did not include a control group.
- Outcome measures: Studies were included if they used a SRTT and reported response times for repeated trials against response times for random trials. Studies using other tasks (mirror tracing, etc.) were not included.

Quality of included studies

We assessed all papers for study quality using 10 criteria: (1) sample size (group of at least 15 participants), (2) matching between control and experimental groups (at least age, sex, cognitive level), (3) evaluation of the cognitive skills (IQ, autonomy, etc.) of the participants, (4) detail on SRTT protocol (at least: number, detail, and type of blocks, sequence, stimulus format, hands used), (5) random block added at the end of the protocol, (6) measured variables include at least response time and accuracy, (7) specify whether or not the participants were under treatment, (8) statistical analysis of the independent variables is presented, (9) an effect size is given, and (10) the limits of the research are discussed in conclusion. Each article was assigned a score from 0 to 10. This score determines a level of quality of the data reported in the article: a grade greater than or equal to 8 corresponds to a high quality, a grade between 5 and 7 (5 included) denotes a moderate quality, and a grade below 5 corresponds to a low quality.

Results

Four hundred seventy-three articles were identified through the selection procedure presented in Fig. 2. After correction of duplicates, titles and abstracts were selected; 284 studies were excluded. The full text of 183 studies was evaluated for eligibility: 9 studies were not about population of interest, 30 are not about PPMLS, 14 studies did not meet the inclusion criteria because they were not compared to a control group, 87 studies were excluded because the authors did not use the SRTT or did not compare response times for sequential trials with response times for randomized trials, and 5 are reviews or meta-analyses. Finally, a total of 39 original studies were included and analyzed. We have consulted the 5 meta-analyses and the review to check our list.

A majority of the studies measured the impact of PD on PPMLS ($n = 28$ original studies). Eight studies focus on PPMLS in AD (including 7 original studies), and 8 original studies focus on CD lesions. Among these studies, 2 studies compare PPMLS during SRTT tasks in patients with AD, patients with PD and control participants and 2 studies in patients with PD, patients with CD and control participants. Two independent assessors (EM and CSB) rated the quality of the 42 original studies. There was complete consensus between the two assessors at global rating level.

Four papers were coded as a high quality, 27 as a moderate quality, and 12 as a low quality.

Results of original studies are reported in Table 1 to CD, Table 2 to AD, and Table 3 to PD.

As illustrated in Table 1, results in CD participants are very heterogeneous. Two studies find a preservation of PPMLS in cerebellar lesions [40–42]. For 2 studies, the PPMLS was impaired but preserved under certain conditions [41, 43], and finally 4 studies have shown that cerebellar patients exhibited no evidence of learning the sequence [44–47].

As illustrated in Table 2, the literature on PPMLS in AD (5 studies on 7) concludes that PPMLS is preserved in this disease [48–53]. Learned sequence is also retained in long-term memory in AD [50].

As illustrated in Table 3, studies indicate an alteration of PPMLS in PD. Kemény, Sommer, and Stefanova [54–56] found no significant evidence of motor sequence learning. Other results are more contrasted. Motor learning is possible for patients with PD, but it is less reliable or requires a longer learning period [45, 57]. Two studies found evidence of PPMLS in patients with PD [58, 59]. It appears that several factors need to be considered to assess PPMLS in patients with PD.

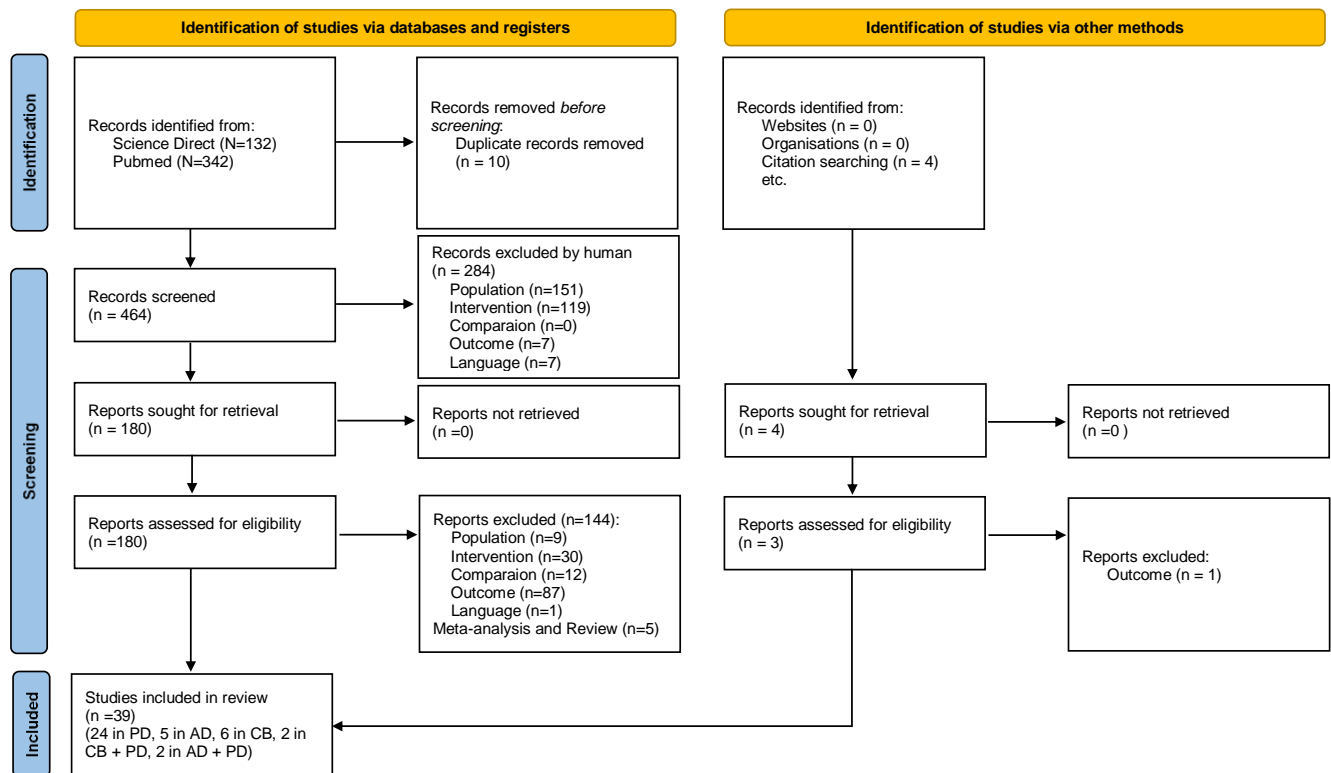


Figure 2 : PRISMA flowchart showing the process of identifying articles for the review

The present systematic review aimed to give a comprehensive picture of deficits in the early and late stages of PPMLS assessed by the SRTT in lesions of the stria-tum (i.e., Parkinson’s disease, PD), the hippocampus (i.e., Alzheimer’s disease, AD), and the cerebellum (i.e., cerebellar disease, CD). First of all, our results suggest that the literature is largely more abundant on PD compared to AD or CD, and in early stage than in late stage of PPMLS. Today, the models of Doyon et al. [23] and Hikosaka et al. [24] present different aspects of PPMLS with an emphasis on perceptual and motor learning in the first one and on early and late phases of learning for the second one. The results of our systematic review suggest that patients with PD present impaired motor learning, whereas patients with CD and AD present impaired perceptual learning. Hence, as summarized in Fig. 1A, the striatum may have a crucial role in motor learning at the late stage while the cerebellum and hippocampus may have a crucial role in perceptual learning at the early stage of PPMLS (Fig. 1B). The second result of our review is that PPMLS is influenced by a combination of personal and task’s characteristics. A complete picture of these factors is discussed below.

Early and late stages of PPMLS

As discussed in the “Introduction,” PPMLS is known to go through different stages: a fast (early) stage, a slow (later) stage, a consolidation stage, an automatic stage and a retention stage [23]. Janacek [28] proposed that the first day of SRTT training can be considered as the early stage of sequence learning and so later stage occurs in a second day of SRTT training. If this distinction is considered, then the majority of studies focus on the early stage of learning rather than the later stage. However, some studies have proposed the use of an interferent task to test the consolidation stage. We did not find any studies that focused on all stages of learning. Concerning the early stage, only one study directly compared PPMLS in PD and CD [46]. Patients with PD show signs of PPMLS, whereas patients with CD failed to show signs of PPMLS. Results were similar when the same protocol was administered to both populations, although the two groups were not directly compared [45]. Only two

articles compared PPMLS in AD and PD [49, 52]. If we consider the level of severity of AD (mild versus very mild), PPMLS is more impaired in patients with AD than in patients with PD [49]. This reflects a more rapid early deterioration of PPMLS in patients with AD. These results on the early stage of PPMLS confirm the important role for the cerebellum and the hippocampus in the early stage of PPMLS.

Table 1 Summary of SRTT characteristics and participant’s characteristics in CD studies. Studies are presented in alphabetical order. (S=sequence block, R=random or pseudo-random block)

Study	Quality	Mean age (years)		Severity disease	Learning	Design protocol						Key findings
		Study group	Control group			Hand	Stimuli	Block	Switch to next stimuli	Repetition of sequence per block	Sequence	
Dimberger et al. 2010 [40]	Moderate	46 ± 15 (N= 11)	45 ± 14 (N= 13)	Isolated ischemic cerebellar infarction in the left (n = 3), right (n=4), or both (n=4) cerebellar hemispheres	Implicit	Bimanual Four fingers	White four horizontally aligned boxes	Experiment 1: training—RPRIR-PRIR-PRIRP—generate Experiment 2: training—RPR RPR RPR RP	Response + 200 ms	Practice blocks (P): 10 × 10 stimuli Interference blocks (I): 10 × 10 stimuli Random blocks (R): 16 stimuli	2,142,314,134 (Practice block)	PPMLS is preserved in patients with CD before interference but it altered after interference. Scores in cognitive-executive functions do not significantly correlate with the degree of interference
Dimberger et al. 2013 [41]	Moderate	47 ± 15 (N= 10)	43 ± 14 (N= 12)	Isolated ischemic infarction in the left (n = 3), right (n=4), or bilateral (n=3) cerebellar hemispheres	Implicit	Bimanual Four fingers	White four horizontally aligned boxes	PRLTRLR-TRLRTRL-RTR	Response + 200 ms	Learning block: 45 × 10 stimuli Random blocks: 90 stimuli Test block: learning sequences, or mirror-inverted learning sequence, or new sequence 45 × 10 stimuli	2,142,314,134 New sequence: 3,423,121,324	PPMLS was reduced for the patients with CD. The patients with CD showed a specific inability to learn the sequence of visual stimuli, whereas their ability to learn the sequence of movements was retained

Table 1 (continued)

Study	Quality	Mean age (years)		Severity disease	Learning	Design protocol					Key findings	
		Study group	Control group			Hand	Stimuli	Block	Switch to next stimuli	Repetition of sequence per block		Sequence
Molinari et al. 1997 [44]	Moderate	Right lesions: 54.66 (range 32 to 75 years) (N=3) Left lesions: 38 (range 20 to 48 years) (N=5)	42.5 (range 26 to 68 years) (N=6)	Focal cerebellar lesions	Experiment 1–2: implicit Experiment 3: Visual learning, not motor response are required Experiment 4: explicit	Unimanual Right hand (RH)+ left hand (LH)	Asterisk appeared in one of four aligned squares	1:R 2–5:S 6: R	Correct response + 500 ms	Experiment 1: 10×8 stimuli Experiment 2: 10×10 stimuli Experiment 3: 10×8 stimuli Experiment 4: 10×10 stimuli	Experiment 1: 43,214,341 (RH) 21,241,324 (LH) Experiment 2: 2,431,342,134 (RH) 3,132,432,134 (LH) Experiment 3: 34,142,314 Verbal response Experiment 4: 4,231,324,321 (RH) 4,143,432,434 (LH)	Unilateral cerebellar lesions severely impair PPMLS, regardless the hand used and the degree of post-lesion motor disturbance (Experiment 1–3). When the sequence was learned before testing, PPMLS is significantly improved in patients with CD (Experiment 4)
Pascual-Leone et al. 1993 [45]	Moderate	57 (30 to 74 years) (N=15)	57 (range 30 to 73 years) (N=30)	5 olivopontocerebellar atrophy + 10 cerebellar-cortical atrophy	Implicit-explicit	Bimanual	Classical SRTT	1:R 2–5:S 6: R	Correct response	Phase I: 10×8 stimuli Phase II: 10×10 stimuli Phase III: 10×12/10 stimuli	Pseudo-random 4–2–3–1–3–2–4–3–2–1	No PPMLS in patients with CD
Shin and Ivry 2003 [46]	Low	64 (49 to 76) (N=8)	71 (range 60 to 89) (N=10)	6 focal lesions = 3 in left/3 in right hemisphere 2 bilateral lesion	Implicit	Main ipsilateral	Classical SRTT + temporal sequence	for the spatial and temporal dimensions: S; R; (P=phase shift)	Correct response + 200, 500, or 800 ms	7×8 stimuli	Pseudo-random 14,213,243	No PPMLS in patients with CD
Spencer et Ivry 2009 [42]	Moderate	Experiment 1: 60.8 years ± 11.8 (N=7) Experiment 2: 57.8 years ± 9.9 (N=10)	Experiment 1: 65.3 years (N=8) Experiment 2: 67.9 years (N=13)	Mixed etiology	Implicit	Experiment 1: Unimanual (tactile screen) Experiment 2: Bimanual (keyboard)	White four circles positioned in the four corners	Experiment 1: 1, R; 2–7, S; 8, R; 9, S Experiment 2: 1–2, R; 3–7, S; 8, R; 9, S; 10, R	450 ms	Experiment 1: 7×8 stimuli Experiment 2: 7×8 stimuli	24,134,231 14,213,243	PPMLS is impaired only the task involving a stimulus–response translation When the stimuli directly indicated the response location, PPMLS is preserved

Only one study distinguished between early and latestages in PD with 2 days of testing [60]. Early learning wasimpaired by dopaminergic medication but not late learning. The findings revealed a differential contribution of the striatal loops during the time-course of PPMLS. Accordingto the authors, the early stage may rely on anterior striatal loop activation. Given that this structure is preserved at the beginning of the pathology, the medication would cause anoverdose that would interfere with PPMLS. The late stage seems to rely on posterior striatum activation.

Motor consolidation refers to a stabilization of the sequence and a reduction to susceptibility to interference. Patients with PD appear to be particularly sensitive to interference; contrary to controls, PD patients cannot decrease their reaction times when performing a previously learned sequence after an interfering sequence [61]. This suggest animpaired consolidation in PD. One study tested the effectof CD on the consolidation of PPMLS [40]. Results suggested that both patients and controls acquired the sequences(although patients were always slower), but only controls were able to reduce their reaction times after the interferingsequence. This suggests an impairment of consolidation in patients with CD [40]. According the authors, this implies that consolidation could be mediated by the cerebellumin addition to the striatum [40, 61]. However, no protocol allows to conclude on the impact of CD. Moreover, it seemsimportant to no study has tested the effect of a 4/6-h delay between early learning and retention. Thus, we cannot conclude on the consolidation as defined by the models used here. Future studies should focus on the later stages to measure the impact of brain lesions on consolidation.

As regards to the retention, Knopman's (1991) study found (after excluding three patients with AD and 2 control participants who presented impaired learning in thefirst session) that patients with AD exhibited similar retention to control participants two weeks later, even if patient with AD group learned less than the control group in the first learning session. The preserved retention in patients with AD suggests that retention may not be mediated by thehippocampus.

To summarize, we find an impact of PD, CB, and AD onthe early stage and an impact of PD and CB on the late stage. These results suggest a probable involvement of the anterior striatum, the cerebellum, and the hippocampus in the early stage of PPMLS and a probable involvement of posterior striatum and cerebellum in the late stage of PPMLS.

Perceptual and motor stages of PPMLS

In the models of Hikosaka et al. (2002) [24] and Van Tilborg's study (2010) [51], perceptual learning (the sequenceof stimulus locations learning) would occur at the early stageof learning and would be associated with a decrease of errors (accuracy), while motor learning (the sequence of fingers tapping on the keys learning) would occur later and would beassociated with a decrease in reaction times (speed). Studiesrevealed that accuracy is impaired in early AD, as revealed by higher error rate and no real improvement during practice[52, 53], whereas change in reaction time is more alteredin PD [55, 62]. The lack of errors decrease in AD suggests that perceptual learning of the visual sequence would be altered in AD [53]. On the contrary, the decrease of errors inPD suggests that perceptual learning of the visual sequencewould be preserved in PD [55, 63]. However, the lack of a decrease in their reaction time could suggest an alterationin motor learning in PD. The study of Helmuth et al. (2000) [64] directly tested this dissociation between perceptual and motor learning in PD and in control participants. Participants had to learn a repetitive sequence of stimulus locationsor a sequence of fingers tapping on keys. Results revealed that patients with PD were able to learn spatial regularities but not motor response regularities, hence confirming the possibility of a preserved perceptual learning and an impaired motor learning in PD.

Finally, the decrease errors and RT during PPMLS itis not very clear in CD. In some studies, both errors and reaction time were impacted [42, 43, 45]. For other studies,only reaction time was impacted [40, 41, 44, 47]. Moreover,some studies did not always measure errors [40, 41]. Perceptual and motor learning have also been tested separatelyin CD [41]. Contrary to control participants, patients with CD showed signs of learning only in the condition involving motor learning and not in perceptual learning (this is reflected in the RT, but the authors did not report the error rate). What would be problematic would be learning the sequence of visual stimuli and not motor response regularities [41]. When patients with CD were asked to visually look at the sequence

without motor production and to verbally recall the sequence, patients with right cerebellar lesions recalled 60% of the sequence while patients with left cerebellar lesions recalled 40%, compared to 100% of the sequence for controls. This result suggests that patients with focal CD are affected in detecting a visual sequence [44]. These data suggest that the cerebellum would be more involved in the detection of the order of events than in the planning of movements. Beyond the role of the cerebellum in motor control, it would also be implied in cognitive aspects of PPMLS. In line with this idea, previous work suggests that the cerebellum may allow formation and use, but not of storage of procedural strategies [44]. The cognitive role of the cerebellum has been argued in previous studies [42] and models [65–67].

All these data suggest that the role of the cerebellum and hippocampus in PPMLS may be more crucial in perceptual learning, which requires the detection of the sequence of stimulus locations, whereas the role of the striatum would be primordial in planning of regular motor responses. Thus, as illustrated in Fig. 1, experimental results on the effects of neurological diseases on different stages of PPMLS help to clarify the models of Hikosaka [24] and Doyon et Benali [23].

Table 2 Summary of 7 SRTT characteristics and participant's characteristics in AD studies. Studies are presented in alphabetical order. (MMSE=Mini-Mental State Examination, MDRS=Mattis Dementia Rating Scale, S=sequence block, R=random or pseudo-random block)

Study	Quality	Mean age (years)		Severity disease	Design protocol							Key findings
		Study group	Control group		Learning	Hand	Stimuli	Blocks	Switch to next stimulus	Repetition of sequence per block	Sequences	
Ferraro and al. (1993) [49]	Low	73.35 (N=42)	70 (N=26)	Very mild (N=27) CDR=0.5 Mild (N=15) CDR=11	Implicit	Bimanual	Asterisk appeared in one of four aligned positions	1-4: S 5: R	Correct answer + 500 ms	10 × 10 stimuli	<i>Not reported</i>	AD does not impact general learning Very mild dementia does not affect specific learning, mild dementia affects specific learning
Grafman and al. (1990) [77]	Low	65.7 ± 9.8 (N=42)	63.9 ± 9.1 (N=44)	Mild to moderate	Implicit	<i>Not reported</i>	Asterisk appeared in one of four aligned positions	1-2: R 3-6: S 7: R	Correct answer then 500 ms	10 × 10 stimuli	<i>Not reported</i>	AD does not affect PPMLS
Knopman and Nissen (1987) [68]	Moderate	70.4 (N=35)	68.5 (N=13)	MMSE from 8 to 25	Implicit	<i>Not reported</i>	Asterisk appeared in one of four aligned positions	1-4: S 5: R	Correct answer then 500 ms	10 × 10 stimuli	<i>Not reported</i>	Overall, AD does not affect PPMLS But 2 subgroups, learners and non-learners, can be distinguished in the spatial subtests of WAIS and Porteus mazes but not in the MMSE

Table 2 (continued)

Study	Quality	Mean age (years)		Severity disease	Design protocol							Key findings
		Study group	Control group		Learning	Hand	Stimuli	Blocks	Switch to next stimulus	Repetition of sequence per block	Sequences	
Schmitz and al. (2014) [51]	Moderate	79.4 ± 4.6 (N=14)	78.8 ± 6.4 (N=14)	MDRS: 118.6	Explicit 2 conditions: errorful errorless	Bimanual	Blue star in one of four aligned positions	Learning phase 1: AA/CC Intermediate SRTT: ABA/CDC Learning phase 2: AA/CC Final SRTT: ABA/CDC	250 ms	10 × 6 stimuli × 2 conditions (errorless/errorful)	A: 134,232 B: 124,323 C:312,414 D:342,141	In RTs, errorless learning advantage is observed in the intermediate SRTT for 2 groups, and only in AD in final SRTT
van Tilborg and al. (2010) [52]	Moderate	79.5 ± 10.1 (N=8)	78.3 ± 6.4 (N=12)	MMSE: 19.6 ± 2 exclusion if < 17	Implicit	Not reported	Asterisk appeared in one of four aligned white squares	1: R 2-5: S 6: R	Correct response + 500 ms	10 × 10 stimuli	4,231,324,321 (pseudo-random)	AD does not alter RTs but increases the errors rate

Table 3 Summary of SRTT characteristics and participant's characteristics in PD studies. Studies are presented in alphabetical order. (S=sequence block, R=random or pseudo-random block, FOC= first-order conditional sequence, SOC= second-order conditional sequence, MRI=magnetic resonance imagery)

Study	Quality	Mean age (years)		Severity disease stage	Treatment	Design protocol experimental							Key findings
		Study group	Control group			(Hoehn-Yahr scale)	Learning	Hand	Stimuli	Blocks	Switch to next stimulus	Repetition of sequence per block	
Brown et al. (2003) [83]	Moderate	G1 (pre-op): 54.9±8.9 (N=10) G2 (post-op): 57.4±7.2 (N=8)	57.2 ± 14.8 (N=10)	Not reported	OFF	Implicit	Control: dominant G1: choice G2: contralateral to the surgery	A solid square dot in one of four horizontally aligned boxes	1–2: R 3–8: S 9: R 10: S	Not reported	8 × 10 stimuli	4,312,413,142	Pallidotomy delete PPMLS in patients with PD
Deroost et al. (2006) [70]	Moderate	66.6 ± 5.73 (N=16)	65.9 ± 6.04 (N=16)	Stage III (3)	ON	Implicit	Bimanual	A black dot in one of four horizontally aligned white squares “Error” is presented when incorrect response	1–9: S 10: R 11: S	Interval of 50 ms	75 × 12 stimuli × 2 sequences (FOC/SOC)	SOC: 12,134,231,424 FOC: 132,342,134,142	FOC and SOC sequence learning in faster patients with PD are comparable to FOC and SOC sequence learning in the control group. In contrast, FOC and SOC sequences learning were severely impaired in slower PD patients
Dominey et al. (1997) [58]	Low	51.9 ± 11.6 (N=7)	55.3 ± 6.9 (N=6)	Stage I to III (2.09)	Not reported	Explicit (authors shown an analogical schema)	Not reported	A square illuminated among 8 square targets placed in square	1: R 2: Seq 1 3: Seq 2 4: Seq 3 5: R	Correct response	5 × 24 stimuli	Unpredictable (u) and predictable stimuli (p) Analogical schema = p, p, u repeated 8 times	Patients with PD are able to learn a simple form of PPMLS under conditions of explicit learning with external error feedback
Ferraro et al. (1993) [49]	Low	69 (N=17)	70 (N=26)	Not reported	Not reported	Implicit	Bimanual	Asterisk appeared in one of four aligned positions	1–4: S 5: R	Correct answer + 500 ms	10 × 10 stimuli	pseudo-random	PD reduces PPMLS

Table 3 (continued)

Study	Quality	Mean age (years)		Severity disease stage (Hoehn-Yahr scale)	Treatment	Design protocol experimental						Key findings	
		Study group	Control group			Learning	Hand	Stimuli	Blocks	Switch to next stimulus	Repetition of sequence per block		Sequence
Helmuth et al. (2000) [64]	Moderate	58.8 ± 10.9 (N=24)	64.6 ± 9.1 (N=24)	Stage I to III	ON	Implicit	Bimanual	The stimuli were the numbers 1 through 4, appeared in one of the white boxes on the screen, at four symmetrical locations: above, below, to the right or to the left of the fixation cross	1–8: S 9–10: number randomized 11–12: S 13–14: location randomized 15–23: S 24–25: number randomized 26: S	Not reported	7 × 6 stimuli for numbers 6 × 7 stimuli for location of number	2 pseudo-random sequences: Location: top/left/right/bottom/right/left/bottom/top/left/right Number-response: 1-3-4-2-3-2	Moderate PD decreases PPMLS. Severity of disease does not worsen PPMLS impairment. PD does not worsen PPMLS with spatial regularity, but worsens PPMLS with motor response regularity. Stimulus distancing does not worsen PPMLS with spatial regularity in PD
Jackson et al. (1995) [79]	Low	65.6 (N=11)	67.5 (N=10)	Not reported	Not reported	Implicit	Preferred hand (index)	“X” appeared in one of the four squares positioned on two lines	1–2: R 3–8: S 9: S* to RG group and R to PR group	Correct response + 200 ms	6 × 11 stimuli	S = 12,431,421,343 (repeated grammar) S* = 43,143,421,312 or 43,431,314,212 or 42,124,313,431 (same rules than S)	PD deletes PPMLS patients with PD could not use information about the associations between adjacent stimuli
Kelly et al. (2004) [73]	Moderate	61.25 ± 8.69 (N=12)	65.22 ± 4.18 (N=9)	Stage I to III (1.83)	OFF	Implicit	Dominant hand (right)	A white illumination in one of the four horizontally aligned boxes	1–3: R 4–8: S 9: R 10: S	400 ms	10 × 10 stimuli × 2 sequences	Unpredictable sequence (pseudo-random) 4,234,213,241 Predictable sequence (FOC) 4,132,142,432	Unpredictable sequence: no learning in PD Predictable sequence: learning in PD
Kemény	Low	62.83 ± 7.9	62.76 ± 7.86	Stages III	ON	Implicit	Bimanual	Classical	S1–S11; R12	Correct	12 blocks × 5	SOC	More participants learn in

Table 3 (continued)

Study	Quality	Mean age (years)		Severity disease stage	Treatment	Design protocol experimental						Key findings	
		Study group	Control group			(Hoehn-Yahr scale)	Learning	Hand	Stimuli	Blocks	Switch to next stimulus		Repetition of sequence per block
Kwak et al. (2012) [61]	High	63 ± 8 (N=17)	63 ± 7 (N=21)	Stage I to II	ON and OFF	Explicit	Bimanual	“X” appeared in one of the four aligned boxes	1: R 2-4: S 5: R	200 ms	6 × 6 stimuli	132,342 (pseudo-random)	Compared with patients OFF medication, patients ON medication showed a significantly reduced drop in RT across the early learning phase. RT decrease in patients OFF was similar to that of healthy controls MRI results showed that medication changes neural recruitment during the early phase of sequence learning
Meissner et al. (2018) [61]	Moderate	53 ± 7 (N=20)	54 ± 8 (N=20)	Stage III	ON	Implicit	Dominant hand (right)	A blue light bar in one of the four horizontally aligned black bars	1: R 2-3: S 4: R 5: S	Correct response + 2 s	10/15 × 8 stimuli	42,134,312 (pseudo-random)	PPMLS relies on suppression of motor-cortical beta oscillations, while stabilization of the learned sequence might be related to motor-cortical theta activity. Both processes are impaired in PD
Meissner et al. (2019) [71]	Moderate	53 ± 7 (N=20)	54 ± 8 (N=20)	Stage III	ON	Implicit	Dominant hand (right)	A blue light bar in one of the four horizontally aligned black bars	1: R 2-3: S 4: R 5: S	Correct response + 2 s	10/15 × 8 stimuli	42,134,312 (pseudo-random)	PPMLS is reduced in PD. Contribution of pre-stimulus motor-cortical beta power suppression to motor sequence learning

Table 3 (continued)

Study	Quality	Mean age (years)		Severity disease stage	Treatment	Design protocol experimental							Key findings
		Study group	Control group			(Hoehn-Yahr scale)	Learning	Hand	Stimuli	Blocks	Switch to next stimulus	Repetition of sequence per block	
Pascual-Leone et al. (1993) [45]	Moderate	56 (N=20)	57 (N=30)	Stages II to III	ON et OFF	Implicit (Expe 1 and 2) and Explicit (Expe 3)	Bimanual	Asterisk appeared in one of four aligned positions	Experiments 1 and 2 1: R 2-5: S 6: R Experiment 3 1-4: S 5-7: R 8: S 9: R	Correct response + 500 ms	Expe 1: 10 × 10 stimuli - Expe 2: 10 × 8/10/12 stimuli Expe 3: 10 × 10 stimuli	Expe 1: Not reported Expe 2: 3 sets: 8, 10 and 12 stimuli Expe 3: 4,231,324,321	Experiment 1: Patients with PD acquired procedural knowledge with a lower rate than control participant Experiment 2: The longer the length of the sequence, the more performance is affected Experiment 3: More practice is necessary in PD. The percentage of patients with PD that reached declarative knowledge was significantly lower than in controls
Pascual-Leone et al. (1994) [59]	Low	63 (N=6)	60 (N=10)	Stage III and IV	ON	Implicit	Dominant hand (right)	Asterisk appeared in one of four aligned positions	1-5: S 6: R	<i>Not reported</i>	10 × 10 stimuli	Pseudo-random	PD does not affect PPMLS
Seidler et al. (2007) [62]	Moderate	57.4 ± 8 (N=8)	59.2 ± 7.4 (N=6)	<i>Not reported</i> Mild to moderate disease	OFF	Implicit	Right hand in phase with distractors, then right and left hand in phase without distractors	“X” appeared in one of the four aligned boxes	Phase 1 (with distractors): 1: R 2-5: S 6: R: Phase 2 (without distractors): 7: R 8: S 9: R Phase 3: ST, second hand 10: R 11: S 12: R	<i>Not reported</i>	94 × 12 stimuli	Pseudo-random	Patients with PD are able of PPMLS, as measured in terms of errors, and are able to transfer learning between hands. If PPMLS is measured in terms of RT, general learning is affected with distractors but not without distractors. Specific learning is altered

Table 3 (continued)

Study	Quality	Mean age (years)		Severity disease stage	Treatment	Design protocol experimental							Key findings
		Study group	Control group			(Hoehn-Yahr scale)	Learning	Hand	Stimuli	Blocks	Switch to next stimulus	Repetition of sequence per block	
Sommer et al. (1999) [55]	Moderate	55.9 (N=11)	51.7 (N=15)	Not reported	OFF	Implicit	Not reported	Asterisk appeared in one of four aligned positions	1-2: R 3-6: S 7: R	Not reported	10 × 10 stimuli	3,241,234,321 (pseudo-random)	PD affects PPMLS measured in RT Explicit retrieval of the tasks (verbal and manual) are comparable in patients with PD and controls
Stefanova et al. (2000) [56]	Moderate	49.2 ± 5.6 (N=39)	48.2 ± 9.6 (N=31)	Stage I to II (1.6)	Not reported	Implicit	Bimanual	A white illumination in one of the four horizontally aligned boxes	1-4: S 5: R 6-8: S	Correct response + 500 ms	10 × 10 stimuli	1,312,432,413 (pseudo-random)	PD affect PPMLS in the early phase, but not declarative knowledge of sequence
Stephan et al. (2011) [57]	Moderate	65.0 ± 9.0 (N=39)	61.0 ± 10.0 (N=39)	Stage I to III	ON and OFF	Implicit	No affected hand	A row of four lights	1-3: R 4: S1 5: S2 6: S1 7: S2 8: R	Correct response then 500 ms	10 × 10 stimuli	S1: 4,324,231,213 S2: 2,324,313,421 (pseudo-random)	PD slows down PPMLS. PPMLS was correlated with stage of disease and axial manifestations. Medication dose is negatively correlated with PPMLS
Tzvi et al. (2021) [82]	Moderate	64.3 (N=16) 46-77	62.6 (N=62.6) 53-77	UPDRS 5 to 39	On	Implicit	Bimanual	Red color appeared in four squares presented horizontally	3 sessions* (R-S-R-R-S-R)		R=24 stimuli S=8 * 12 stimuli	1-2-1-4-2-3-4-1-3-2-4-3	General learning: controls decreased RT across block, PD could not Specific learning: absent in both PD and controls when assessed with RT, but it was present when assessed with error-rates

Table 3 (continued)

Study	Quality	Mean age (years)		Severity disease stage	Treatment	Design protocol experimental							Key findings
		Study group	Control group			(Hoehn-Yahr scale)	Learning	Hand	Stimuli	Blocks	Switch to next stimulus	Repetition of sequence per block	
Werheid et al. (2003a) [74]	Moderate	60.2 ± 7.9 (N = 11)	58.9 ± 5.7 (N = 11)	Stages II to IV	ON	Implicit	Bimanual	The capital letters W, S, F, X, G, H, N, and P were centrally presented on a computer screen	1: R	Response + 500 ms	64 × 8 stimuli	Letter sequence condition WGNFSXPH Location sequence condition 17,465,283	Patients with PD presented reduced sequence-specific learning only in location sequence condition
		60.3 ± 4.5 (N = 12)	59.3 ± 4.1 (N = 11)	Stages II to IV					2–4: S 5: R 6–8: S 9: R 10–12: S 13: R 14–16: S 17: R 18: S				

Personal and task's characteristics influencing PPMLS

All the results reveal a large intra-group heterogeneity in PPMLS results. Several factors other than the brain lesion location can modulate PPMLS. We present the main highlights below but a more detailed analysis of the effect of personal and task characteristics can be found in supplementary data.

As regards *personal characteristics*, some studies failed to find a link between cognitive functions (semantic memory, executive functions) and the PPMLS; however, there is a link between perceptual reasoning (measured by the WAIS subtests) and the PPMLS in AD and CD patients [40, 68].

In CD, heterogeneity can be related to *personal characteristics* such as nature de la lesion (global or unilateral focal) or level of ataxia. No relationship was found between executive function, motor execution, temporal control, and PPMLS. Also, the question of the effect of the etiology, the nature of the lesion, and the disease severity on different stages of PPMLS remains to be explored. As regards *task's characteristics*, the hand used to perform the task seems to impact the PPMLS. When patients used the hand contralateral to the lesion, they presented preserved PPMLS. In contrast, PPMLS was altered when patients performed with the hand ipsilateral to the lesion [43, 46]. Surprisingly, none of the studies which we have identified sought to specify the involvement of the PPML according to the lobe location of the lesion. These results suggest that PPMLS would depend on the side of the lesion and of the hand used. However, another study found that PPML is impaired in CD regardless of the hand used [44]. Hence, results on the effect of the side of the lesion are not unanimous. Further studies are required to understand this effect, but also to take into account the respective roles of the anterior and posterior part of the cerebellum. Even if, to our knowledge, no study has examined this question, it would be interesting to distinguish the anterior vs posterior cerebellar role in PPMLS, as these two parts of the cerebellum seem to be implied in sensorimotor vs cognitive functions, respectively, as reported in the models of Schmahmann [65] and Diedrichsen [67].

PPMLS could be impaired only in tasks involving a stimulus–response translation (when the response is given on the keyboard), but preserved when the stimulus directly indicated the response location (i.e., when the response is given on a touch screen) [42]. Sequence length appears to have little impact on PPMLS, CD patients able to learn sequences of up to 10 items [40, 41]. In AD, some patients are unable to perform the SRTT [50, 53, 68]. From the mild stage of dementia, patients can perform a task but PPMLS was significantly impaired [49]. As regards *personal characteristics* more than memory level, the level of nonverbal reasoning is strongly associated with PPMLS [68]. About *task's characteristics*, only one study compares learning conditions. Schmitz [51] compared errorless and errorful learning conditions. In the errorful condition, participants had to discover the sequence, thanks to a beep sounded if they made a mistake whereas they had visual stimuli as in the classic SRTT in the errorless condition. Learning was greater in the errorless than in the errorful in AD [51]. Given that all other studies used a classic SRTT, we cannot conclude about how other characteristics of the task could impact PPMLS in AD.

In PD, a previous meta-analysis [34] suggested that heterogeneity of results could be explained by the interaction of several factors including (1) dual task condition and (2) long sequence or exposure to sequence ranges or high proportion of ambiguous sequences or symptom severity. But, this meta-analysis has been conducted only in PD and our results highlight other factors relative to personal or task characteristics. As regards *personal characteristics*, deterioration in PPMLS is specifically related to the deterioration in gait and posture [57, 69], and to the slowness and freezing [61, 70–72] rather than to disease severity. PPMLS was not associated with global cognitive status in PD, but with executive and non-verbal reasoning [69, 70, 72]. It is interesting to note similar results in CD and AD [40, 68]. Medication could also be a factor to consider, but its impact seems to depend on the learning stage (impairment during the early but not late stage) [60]. As regards *task's characteristics*, it is difficult to conclude about the superiority of explicit vs implicit learning conditions in PD. The presence of a feedback [58], of a shorter sequence [45], and predictability of sequence [58, 73] seem to facilitate PPMLS in PD. In contrast, the spatial nature of a stimulus deteriorates PPMLS in PD [72–74].

Consistent results revealed that dualtask affects PPMLS in PD patients with freezing, but not PPMLS in PD patients without freezing [72, 73].

Conclusion

Nowadays, PPML is explained by two separated theoreticalneuroscientific models: one focusing on stages and features(perceptual and motor learning) of sequence learning [23] and the other on stages and types of learning (adaptationvs sequence) [24]. Our systematic review highlights that deficits observed in neurological diseases involving lesionsof the cerebellum, the hippocampus, and the striatum (CD, AD, PD) is a good way to provide an integrated model of cerebral structures involved in the time course of PPML. What we know from our systematic review is that perceptual learning is predominant in early stage with implication of cerebellum and hippocampus while motor learning occurs inlate learning with the involvement of the posterior striatum(Fig. 1B). Moreover, in addition to the disease, our systematic review provides an exhaustive panel of personal and task's characteristics explaining the heterogeneity of resultsacross studies on PPMLS.

As regards a more applied perspective, our findings bringinformation to explain why patients may present different levels of PPML despite a same disease. The disease itself gives a general pattern of learning impairment that can be predicted for one patient with CD, AD, or PD. But the characteristics of the individual and of the task to be learned must be considered in order to explain the individual patternof learning impairment and to propose specific and individualized approach for rehabilitation. In line with recent findings indicating that motor learning principles must be applied in rehabilitative intervention [76], we assume that the individual pattern of learning impairment allows to adaptintervention: if PPML is intact, it can support the rehabilitation based on specific and intensive training of the requiredtask. If PPML is impaired, compensation tools and alternative strategies can be proposed to achieve the required task and activities.

Declarations

Conflict of interest The authors declare no conflict of interest.

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