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A complexidade de obras de arte afeta a percepção subjetiva do tempo e atividade motora bimanual desempenhada na ausência e na presença de música de pacientes com doença de Parkinson

The complexity of an artwork affects the subjective perception of time and bimanual motor activity performed in the presence and absence of music of the patients with Parkinson's disease

Márcia Regina Motta

Tese apresentada à Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto da USP, como parte das exigências para a obtenção do título de Doutora em Ciências, Área de Concentração: Psicobiologia.

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Orientado: Prof. Dr. José Lino Oliveira Bueno

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RESUMO

Motta, M. R. (2021). *A complexidade de obras de arte afeta a percepção subjetiva do tempo e atividade motora bimanual desempenhada na ausência e na presença de música de pacientes com doença de Parkinson* (Tese de Doutorado). Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto.

A passagem do tempo é percebida em um contexto de multitarefa. Pacientes com doença de Parkinson (PcPD), devido a disfunções motoras, cognitivas e perceptivas podem apresentar alterações no julgamento de durações, principalmente quando mais de uma tarefa precisa ser realizada ao mesmo tempo e alguns fatores podem influenciar mais que outros e levar a melhora ou a piora do desempenho. A presente pesquisa tem como objetivo examinar os efeitos da música sobre a percepção do tempo e sobre a manipulação de obras de arte com diferentes níveis de complexidade desempenhada por PcDP nos estados com (ON) e sem (OFF) medicação dopaminérgica. Para isso, duas esculturas diferindo em nível de complexidade, sendo o número de peças o fator diferenciador: obra de arte mais complexa (MaC) contendo 10 peças e obra de arte menos complexa (MeC) contendo 6 peças. Elas foram manipuladas por PcDP e indivíduos sem a doença. A exploração ocorreu na presença ou na ausência de música, durante o intervalo de 45s. O tempo de manipulação foi reproduzido e verbalmente estimado. Os PcDP foram testados primeiro na condição OFF e depois na condição ON de medicamento. A frequência do movimento exploratório foi analisada. Os dados foram submetidos a ANOVA de medidas repetidas modelo misto com $p<0.05$. Os resultados mostraram que o nível de complexidade das obras de arte afetou a percepção do tempo dos participantes. O tempo de manipulação da MaC foi subestimado na reprodução temporal e superestimado na estimação verbal. O tempo de manipulação das MeC, apesar de também ter sido subestimado na reprodução temporal e superestimado na estimação verbal, foi julgado como maior em relação a MaC. Estes resultados foram independentes do grupo, do estado de medicação, e da presença ou ausência de música. Encontrou-se efeito do medicamento sobre a percepção do tempo dos PcDP. Quando em OFF, eles apresentaram desempenho similar aos dos participantes sem a doença, o que não ocorreu estavam em ON. Observou-se o efeito de grupo sobre a frequência de movimentos realizados pelos participantes. Os PcDP apresentaram menor frequência de movimentos do que os participantes sem DP. Apesar disso, o medicamento teve efeito sobre a atividade motora dos pacientes, aumentando a frequência de movimento. Não foi encontrado efeito da música sobre a frequência de movimento e sobre a percepção do tempo dos participantes com e sem DP. Os resultados apontam o efeito que propriedades, tal como nível de complexidade de obras de arte, têm sobre o julgamento temporal de participantes com e sem DP. Para os PcDP, o medicamento pareceu não influenciar o processamento da informação temporal, mas, pareceu afetar a atividade motora. A música mostrou não prejudicar e nem melhorar o desempenho perceptivo e motor dos PcDP. É provável que a complexidade da obra de arte tenha se configurado como um aspecto que reteve a atenção dos participantes e a desviou da passagem do tempo, e a maior frequência de movimentos dos PcDP quando estavam medicados pode ter contribuído para o julgamento temporal.

Palavras-chave: Percepção do tempo. Obra de Arte. Música. Atividade Motora. Doença de Parkinson.

ABSTRACT

Motta, M. R. (2021). *The complexity of an artwork affects the subjective perception of time and bimanual motor activity performed in the presence and absence of music of the patients with Parkinson's disease* (Doctoral Thesis). Faculty of Philosophy, Sciences and Letters of Ribeirão Preto, University of São Paulo, Ribeirão Preto.

The time passage is perceived in a multitasking context. Patients with Parkinson's disease (PwPD) due to motor, cognitive and perceptual disorders may present alterations in the judgment of duration, especially when more than one task needs to be performed at the same time and some factors may influence more than others and lead to improvement or the deterioration of performance. This research aims to examine the effects of music on the time perception and on the manipulation of artworks with different levels of complexity performed by PwPD in conditions with (ON) and without (OFF) dopaminergic medication. For this, two sculptures differing in level of complexity, with the number of pieces being the differentiating factor: more complex artwork (MC) containing 10 pieces, and less complex artwork (LC) containing six pieces. They were manipulated by PwPD and disease-free participants. The exploration took place in the presence or absence of music during the 45s interval. Manipulation time was reproduced and verbally estimated. PwPD were tested first in the OFF condition and then in the ON medication. The frequency of the exploratory movement was analyzed. Data were submitted to a mixed-model repeated measures ANOVA with $p<0.05$. The results showed that the level of complexity of the artworks affected the participants' time perception. MCA manipulation time was underestimated in temporal reproduction and overestimated in verbal estimation. The manipulation time of the LCA, despite also having been underestimated in the temporal reproduction and overestimated in the verbal estimation, was judged as greater in relation to the MCA. These results were independent of the group, medication condition, and the presence or absence of music. There was an effect of the medication on the time perception by PwPD. When in OFF, they performed similarly to participants without PD, which did not happen when they were in ON. The group effect on the frequency of movements performed by the participants was observed. PwPD had lower movement frequency than participants without PD. Despite this, the medication influenced the motor activity, increasing the movement frequency. There was no effect of music on the movement frequency and on the time perception of participants with and without PD. The findings point to the effect that properties, such as the level of complexity of artworks, have on the temporal judgment of participants. For PwPD, the medication did not seem to influence temporal information processing, but it did seem to affect motor activity. The music proved neither impair nor improve the PwPD's perceptual and motor performance. It is likely that the complexity of the artwork was configured as an aspect that retained the participants' attention and diverted it from the passage of time, and the higher frequency of PwPD movements when they were medicated may have contributed to the temporal judgment.

Keywords: Time perception. Artwork. Music. Motor activity. Parkinson's disease.

Summary

1 Introduction

Time is a dimension that permeates human existence, it is past, present, and future. Investigating how we subjectively perceive the passage of time during the performance of our actions in the world is better to know how we experience life and what are the events that cause us to lose track of time and those that make us live eternity in minutes. In the words by Mario Quintana:

> A vida é o dever que nós trouxemos para fazer em casa.
> Quando se vê, já são seis horas!
> Quando se vê, já é sexta-feira!
> Quando se vê, já é natal...
> Quando se vê, já terminou o ano...
> Quando se vê perdemos o amor da nossa vida.
> Quando se vê passaram 50 anos!
> Agora é tarde demais para ser reprovado...
> Se me fosse dado um dia, outra oportunidade, eu nem olhava o relógio.
> Seguiria sempre em frente e iria jogando pelo caminho a casca dourada e inútil das horas...
>
> Life is the duty we bring home.
> When you see it, it's already six o'clock!
> When you see it, it's already Friday!
> When you see it, it's already Christmas...
> When you see, the year is over...
> When we see we lose the love of our life.
> When you see it, 50 years have passed!
> Now it's too late to regret ...
> If I was given a day, another opportunity, I wouldn't even look at my watch.
> I would go on and on and throw the useless golden bark of the hours along the way...

Music is constituted as an event structured in intervals of time, the rhythm. Listening to a music has the potential to awaken memories and “make us dance”. Parkinson's disease patients have a special relationship with music. When listening to music with prominent beats, the patient can “be led to forget their motor limitations” and experience the passage of time in a totally subjective way.

Thus, the present work aims to investigate the effect of music on the time perception and on the manipulation of artworks with different levels of complexity in patients with Parkinson's disease. The hypothesis is that the effect of music on the time perception may be greater in PD patients without medication than in patients with medication., and among PD patients (medicate and no-medicate) when compared to compared to non-PD participants. Furthermore, music may induce the improvement of the motor task of PD patients. Likewise, the different levels of complexity of artworks may influence the temporal duration and the manipulation of artworks by patients.

The result of this work will be presented in chapters in the form of articles. They are: (a) Verbal temporal estimation and temporal reproduction of patients with Parkinson's disease: a systematic review, (b) Immediate effect of auditory stimuli on upper limb movement in patients with Parkinson's disease: a systematic review, and (c) The complexity of an artwork affects the subjective perception of time and bimanual motor activity performed in the presence and absence of music by patients with Parkinson's disease.

2 Verbal temporal estimation and temporal reproduction of patients with Parkinson's disease: a systematic review

The representation of the passage of time is critical for a variety of cognitive, perceptive, and motor activities. For complex movements to be executed properly and higher cognitive functions to be performed, such as decision making and action planning, adequate processing of temporal information is required. Therefore, the human ability to accurately estimate, reproduce and maintain temporal information is fundamental for the management of life in society (Harrington et al., 2011; Koch et al., 2008).

Many methods have been proposed for assessing the temporal judgment of an event. In general, the main objective of using these methods is to verify if the perceived duration approximates the real duration to-be-estimated; or the interest is to identify distortions in the perception of time or problems in temporal processing. In this ground, the literature presents four main methods of temporal estimation to investigate the mechanisms involved in time perception (Grondin, 2010; Mioni et al., 2014; Zakay, 1993): *verbal estimation* is the verbal translation a target interval experienced into temporal units, such as seconds or minutes; *temporal reproduction occurs* when a target interval is presented, and its duration is reproduced by a motor action. For instance, pressing a button to record the beginning and end of the interval. In general, in tasks involving these two methods it is common to find a motor element, that is, motor timing, which is a repetitive and continuous movement, e.g., synchronizing clapping in time with the music, and continuing to clap following the rhythm in the absence of the music, or a repetitive tapping task (Jones & Jahashahi, 2014); *temporal production occurs* when a target interval is previously established in temporal units, then this duration is produced, which can occur through a motor action similar to the one used in temporal reproduction; *method of* *comparison*, such as the temporal discrimination, time intervals are presented successively and it is required to indicate whether the second interval was shorter or longer than the first. Considering these methods of judging the duration of events, researchers that study the time perception have shown interest in better understanding the distortions of temporal perception across specific populations (Allman & Meck, 2012).

In this context in which alterations in the judgment of the duration of an event are investigated, Parkinson's disease (PD) gains special importance. It is a neurologic disorder characterized by the progressive degeneration of dopamine-releasing neurons, resulting in the atrophy of the basal ganglia. These neural structures modulate the control of voluntary movements, decision making, and they engage in the temporal information processing (Cabreira & Massano, 2019). Thus, functional impairments in the dopaminergic system contribute to cognitive, perceptual, and motor disorder related to time perception (Allman & Meck, 2012; Magalhães, et al., 2018; Torta et al., 2010).

The aim of this study was to conduct a systematic exploration of research results on time perception in PD. The focus is on the main findings and on the identification of the aspects involved in the temporal processing of tasks whose judgment methods were verbal estimation and temporal reproduction. Among others, these judgment methods allow the subjective perception of time to occur during cognitive, sensory, perceptual, and motor processes, supporting an ecological perspective.

2.1 Method

Online searches in the MEDLINE and Web of Science (no date limit) databases were initially performed in August 2019 and repeated in January 2021 using relevant terms:

[Parkinson's disease and time perception], [Parkinson's disease and time estimation], [Parkinson's disease and time reproduction].

Study selection

The articles included if the following criteria met: 1) original papers; 2) written in the English language; 3) participants were patients with Parkinson's disease (PD patients); 4) verbal estimation and/or temporal reproduction as methods to investigate the time perception.

Articles excluded if they were 1) reviews, meta-analysis, case reports, dissertations, book reviews, conference, or editorial work; 2) were animal studies.

Study selection, data extraction and analysis

Initially, articles were selected by titles. Next, abstracts were examined and if they appeared relevant, then the full text content was downloaded and analyzed. Also, reference lists of identified articles were searched for additional studies. The selected studies were compared to remove duplicate records. Relevant data such as the title, first author, publication year, participant population (healthy and PD patients), descriptive characteristics of the participants (age, gender, disease stage), number of participants, stimuli used, method of temporal judgment, outcomes and dropouts were extracted by reviewer (MRM) using inclusion criteria. These data were analyzed by the second author (JLOB) and, in case there was disagreement, it was discussed between the two reviewers and, if necessary, the opinion of the third author (VT) was requested.

In sum, the papers included studied the time perception. The study population was composed of PD patients. The interventions were defined as any experimental methodology with the ability to influence the time perception mediated by tasks involving temporal judgment (i.e., verbal estimation and time reproduction). The planned method of analysis for this review was a descriptive synthesis.

2.3 Results

The primary outcome was that PD patients showed impaired reproduction and verbal estimation of the duration of an event. In addition, the characteristics of the applied tasks, the temporal judgment method and the treatment conditions shown to affect the way in which patients perceived the passage of time.

The database search identified eighty-nine unique publications for the combinations of descriptors. These articles were evaluated for eligibility based on title and abstract; thirty-seven papers were classified as meeting the eligibility criteria. The next step in the process involved screening the full text to identify the relevance of the article and subsequently verifying that it met the eligibility criteria. Thus, in total, it was included eighteen papers in this study (Figure 1).

It is important to mention that, although there is a distinction between motor time (considered as a temporal process intrinsically linked to movement) and perceptual time (defined as subjective judgment of time not defined by movement), in our study, both processes of temporal judgment were considered closely related and therefore not distinguished. This is because, in general, an event to-be-estimated involves motor components. In addition, a study found a significant correlation between performance on motor tasks and time perception (Merchant et al., 2008).

Figure 1

Flowchart of study selection process

Identification	1270 studies identified though PubMed and Web of Science database	No additional studies identified though the reference lists
	209 studies selected by title	1061 studies removed
	89 studies after duplicates removed	120 studies excluded
Screening	89 studies screened	
	37 studies selected by abstract	52 studies excluded
Eligibility	18 full text studies assessed for eligibility	19 studies excluded
Included	18 full text studies included in the qualitative synthesis	

Below, the results of this review were described on five topics: (a) models of time perception, (b) memory and attention as cognitive processes involved in time processing, (c) brain structures, timing network and dopaminergic system involved in processing of temporal information, (d) motor activity related to time judgment and (e) overview of selected studies. Also, a comprehensive list of investigations into perceptual timing in PD patients is provided in Table 1.

Table 1

Summary of findings from studies of perceptual time in patients with Parkinson's disease

Study	Medication state	Modality	Motor activity	Standard duration	Results
			Verbal time estimation		
Pastor et al. (1992)	ON & OFF	Visual	Counting	3, 9, 27s	Underestimation
Riesen & Schnider (2001)	ON	Motor	Counting (Random number). Finger tapping	12, 24, 48s	Underestimation
Wearden et al. (2008)	ON & OFF	Auditory	No	77, 203, 348, 461, 582, 767, 834, 958, 1065, 1,183ms	No impairment
Wearden et al., (2009)	ON & OFF	Auditory	No	325, 475, 625, 775, 925, 1,075, 1,225ms	No impairment
Motta et al., (2019)	ON	Motor	Bimanual manipulation	Seconds. Varied for each participant	No impairment
			Temporal Reproduction		
Pastor et al. (1992)	ON & OFF	Visual	Counting	2, 3, 4.5, 6, 9s	Overestimation
Malapani et al. (1998)	ON & OFF	Visual (Peak-interval-10 trials)	Counting (Random number)	8, 21s	Migration effect.**Impairment for 21s (OFF only)
Malapani et al. (1998)	ON & OFF	Visual (Peak-interval-80 trials)	Counting (Random number)	6, 17s	Migration effect (OFF only)
Koch et al. (2004)	OFF & OFF - DBS	Visual	Counting (Random number)	5, 15s	Migration effect
Koch et al. (2004)	OFF & rTMS	Visual	No	4, 5, 6s	Improved when DLPFC stimulated
Koch et al., (2005)	ON & OFF	Visual	Counting (Random number)	5, 15s	Left-hemi PD: migration effect; Right-hemi PD: overestimate 5s (OFF Only)

Study	Medication state	Modality	Motor activity	Standard duration	Results
Koch et al., (2008)	ON & OFF	Visual	No	Short: 400, 450, 500, 550, 600ms Long: 1,600, 1800, 2000, 2200, 2400ms	Experiment 1: underestimation of long intervals Experiment 2: No impairment (1 h delay between short and long trials)
Perbal et al., (2005)	ON	Visual	Counting Condition. Reading condition (during encoding only). Random number	5, 15, 38s	In both conditions: no impairment. Reading condition: increased variability
Jones et al., (2008)	ON & OFF	Auditory	No	250, 500, 1,000, 2,000ms	Underestimation for 2000ms
Torta et al. (2010)	ON & OFF DBS	Motor	Unscrewing a stud nut	Seconds. Varied for each participant	Underestimation (OFF Only)
Wojtecki et al., (2011)	DBS	Auditory	No	5, 15s	Migration effect
Dušek et al., (2012)	ON & OFF	Visual	No	5, 5,95, 7,07, 8,41, 10, 11.89, 14.14, 16.82s	Migration effect. Overestimation for 16.82 s (ON only)
Honma et al., (2016)	ON	Visual	Counting	0.5, 1, 2, 3, 5, 10, 20, 30, 60, 120, 300s	Overestimation for durations below 2 s.
Honma et al., (2018)	ON	Visual		11, 2 s	No impairment (5 min. delay between encoding and decoding)

Note: PD = Parkinson's disease; ON = PD patient medicated; OFF = PD patient no medicated; Migration effect = it occurs when PD patients over-reproduce the short time intervals and under-reproduce long intervals presented in the same task; DBS = Deep brain stimulation; rTMS = Repetitive transcranial magnetic stimulation; DLPFC = Dorsolateral prefrontal cortex.

Models of time perception

Regarding the models of time perception, 13 papers (Honma et al., 2016; Honma et al., 2018; Jones et al., 2008; Kock, Brusa et al, 2004; Malapani et al., 1998; Malapani et al., 2002; Motta et al., 2019; Pastor et al., 1992; Perbal et al., 2005; Torta et al., 2010; Wearden et al., 2008; Wearden et al., 2009; Wojtecki et al., 2011) mentioned approaching temporal perception based on information processing models. The models highlighted by studies share the idea that duration perception is mediated by an internal clock, which captures and accumulates time information to make decisions through comparison with previously stored time duration memory. Thus, cognitive components, that is, memory and attention, seem to play important roles in the processing of temporal information. Furthermore, research on time perception models has identified neurobiological and neurochemical aspects directly involved in the processing of temporal information.

Cognitive processes

About the cognitive processes involved in the time perception, 17 articles (Dušek et al., 2012; Honma et al., 2016; Honma et al., 2018; Jones et al., 2008; Koch, Brusa, et al., 2004; Koch, Oliveri et al., 2004; Koch et al., 2005; Koch et al., 2008; Malapani et al., 1998; Malapani et al., 2002; Motta et al., 2019; Pastor et al., 1992; Perbal et al., 2005; Torta et al., 2010; Wearden et al., 2008; Wojtecki et al., 2011) addressed the subject. Cognitive processes, that is, memory and attention seem to be closely related to temporal judgment. The studies on time perception point to alterations in performance in temporal estimation tasks that would explain memory deficits or reduced attention in PD patients. Meantime, aspects related to the task must be taken into account. Dual-task and double-duration task can directly lead to increased memory load and demand for attention, reflecting on how perceived the time interval.

Processing of temporal information

Neuroanatomical substrates involved in the temporal information processing were discussed in 8 experimental papers (Dušek et al., 2012; Jones et al., 2008; Kock, Brusa et al, 2004; Koch, Oliveri et al., 2004; Koch et al., 2005; Koch et al., 2008; Wearden et al., 2009; Wojtecki et al., 2011). These studies pointed to neural structures that would be involved in temporal judgment. These structures would be in the subcortical and cortical regions, covering mainly the basal ganglia (BG), and frontal cortex. They would be activated according to the temporal task, based on time scales of sub- and supra-second. However, the BG seem to be key pieces for the time perception, as they are activated for both shorter duration intervals (sub seconds) and longer durations (supra seconds).

In relation to temporal brain networks, 6 papers (Honma et al., 2018; Kock, Oliveri et al, 2004; Koch et al., 2005; Koch et al., 2008; Torta et al., 2010; Wojtecki et al., 2011) address the subject. These studies pointed out that, although the BG appear to be a primary brain structure, it is likely that a wide neural network is involved in processing temporal information. However, the neural network activated depends on the task duration, cognitive load, sensory and motor context. Moreover, the authors converge in presenting the cortico-thalamic-striatal-cortical circuit as the network frequently activated in temporal perception tasks.

The relationship between the dopaminergic function and time perception was demonstrated in 16 studies (Dušek et al., 2012; Honma et al., 2016; Jones et al., 2008; Kock et al, 2008; Kock et al, 2005; Kock, Oliveri et al, 2004; Malapani et al., 2002; Malapani et al., 1998; Motta et al., 2019; Pastor et al., 1992; Perbal et al., 2005; Riesen & Schnider, 2001; Torta et al., 2010; Wearden et al., 2008; Wearden et al., 2009; Wojtecki et al., 2011). These studies discussed the effect of dopamine on temporal judgment. They pointed out that dopaminergic levels would modulate the time judgment. In general, a trend observed, an increase in dopaminergic concentration leads to an underestimation of the duration of an event, and a decrease in the dopamine level would lead to an overestimation of the duration of an event. Furthermore, dopamine appears to be related to the cognitive process, i. e., it would affect the level of attention to temporal signals. Specifically, in the PD patients, changes in dopamine function would affect their performance in temporal tasks, but after administration of the dopaminergic drug, there would be an improvement in their performance. However, there is the possibility that the improvement shown by PD patients in temporal judgment tasks is related to the effect of dopamine on motor symptoms and not directly on the temporal processing neural system. Moreover, the heterogeneity in PD, whose individual variability in responsiveness to dopamine replacement therapy would also tend to influence the time perception.

Motor activity

Eight articles (Honma et al., 2016; Jones et al., 2008; Kock et al, 2005; Motta et al., 2019; Pastor et al., 1992; Riesen & Schnider, 2001; Torta et al., 2010; Wearden et al., 2008) presented aspects related to the motor activity of PD patients and its possible influence on the time perception.

It was identifying the motor action present in the counting of time, either internally or aloud, as a factor that would affect the temporal judgment. Likewise, it was questioning the temporal reproduction method, as it could influence the estimation of time due to the motor activity required to record the duration of an event. This is because the impairment of the motor function present in PD and generator of changes in speed and quality of movement would directly affect the duration estimates. However, this assumption did not seem to be supported by findings that indicated that both the time counting, and the temporal reproduction method would not have the potential to cause such interferences in the temporal estimations of PD patients. On the other hand, PD patients showed impairment in the reproduction of the duration of their own motor acts.

Overview of selected studies

In this section, an overview of the studies found was conducted with a focus on highlighting some main factors observed when verbal temporal estimation and time reproduction were used as methods of judging the duration of an event performed by PD patients. This analysis shows that time perception tasks were extremely varied, which contributed to the heterogeneity of the findings in PD.

In the verbal time estimation task, Pastor et al. (1992) found underestimation in PD patients. Motta et al. (2019) and Riesen and Schnider (2001) found no differences in the verbal temporal judgment of PD patients in relation to the control group (CG). However, Motta et al. (2019) reported that participants overestimated time, while Riesen and Schnider (2001) indicated that participants underestimated duration. Other verbal time estimation studies (Wearden et al., 2008; Wearden et al., 2009) found similar performance between PD patients and CG, they were accurate in the time estimation task.

Pastor et al. (1992) found that patients performed better on the verbal temporal estimation task when on ON dopaminergic medication compared to their unmedicated state. However, Wearden et al. (2008) and Wearden et al. (2009) did not report differences in time estimation performance in patients evaluated on OFF and ON dopaminergic medication.

Among the studies that investigated the verbal temporal estimation, two of them included the counting of time as part of the task to be performed, either the internal counting through the presentation of a visual stimulus (Pastor et al., 1992) or the counting aloud simultaneously a tapping task (press the spacebar once a second. Riesen & Schnider, 2001). These works used durations that ranged from 3s to 48s and observed an underestimation of time. In this sense, it was raised an assumption that counting would have affected the time perception as it is a motor action, and PD patients would have impaired motor function.

Considering the temporal reproduction task, a study (Wojtecki et al., 2011) investigated the influence of DBS on time judgment, and another study (Koch, Oliveri et al., 2004) used rTMS in PD patients to observe its effect on a temporal reproduction task.

Among the studies that evaluated the OFF and ON medication conditions in PD patients, five (Honma et al., 2016; Koch et al., 2005; Koch et al., 2008; Malapani et al., 1998; Pastor et al., 1992) reported that the medication had a beneficial effect on at least some of the intervals used. Studies that used DBS to assess PD patients' performance in the temporal reproduction task (Koch, Brusa et al., 2004; Torta et al., 2010) found a positive effect of the treatment condition (ON-DBS and ON medication) on task. While one study (Wojtecki et al., 2011) found a difference in patient performance that was related to stimulation levels.

Furthermore, studies (Dušek et al., 2012; Koch, Brusa et al., 2004; Koch et al., 2005; Malapani et al., 1998; Malapani et al., 2002; Wojtecki et al., 2011) observed that PD patients over-reproduced the short time intervals and under-reproduced long intervals presented in the same task, a phenomenon called *Migration Effect*. These studies, mostly, used visual stimuli, such as the presentation of squares, rectangles, and random numbers on a screen, for durations in seconds. The study that used auditory stimulation (700 Hz tone) found 'migration effect' in PD patients with DBS (Wojtecki et al., 2011).

2.4 Discussion

This review highlight that the time perception of PD patients is not homogeneous and distinct factors can influence it: duration judgment method (verbal or reproduction) associated with the type of task (sensory or motor), type of stimulus (visual, auditory, or motor), duration of the event, medication condition and treatment. Moreover, it is important to consider that the neurological and neurochemical alterations related to the disease add intrinsic factors to the temporal judgment. In this sense, measuring the continuous passage of time is a complex phenomenon influenced by extrinsic and intrinsic factors, which make the task subjective.

The aim of this review was to analyze studies that investigated the verbal estimation of time and the temporal reproduction of PD patients. Thus the following aspects were highlighted: (a) models that propose to explain how the process of time perception occurs; (b) cognitive processing of temporal information, particularly considering memory and attention functions; (c) the motor activity that appears both in the time estimation process (for example, when using motor action to record temporal reproduction), and the motor tasks that are part of the event to have its duration judged; and (d) the neural structure and the neurochemical components involved in the temporal information process. Each of these aspects will be discussed below.

Time perception models

The literature presents several models that purport to explain how the process of time perception occurs. The model mentioned by the studies found in this review (Honma et al., 2016; Honma et al., 2018; Jones et al., 2008; Kock, Brusa et al, 2004; ; Malapani et al., 1998; Malapani et al., 2002; Pastor et al., 1992 Perbal et al., 2005; Torta et al., 2010; Wearden et al., 2008; Wearden et al., 2009; Wojtecki et al., 2011) and appears to be the basic mechanism to explain the temporal perception is the timing theoretical model named the *Internal Timer Model or Scalar Expectancy Theory* – SET (Treisman, 1963). This model assumes that during a 'to-be-timed' experience, pulses are produced at some speed rate by a pacemaker. These pulses are collected by a switch into an accumulator. This pacemaker-switch-accumulator would be the 'perceptual' (or clock) component of the system. The content accumulated by the 'clock', corresponding to the current time, is transferred from working memory or reference memory for long-term storage (memory system). Finally, the estimation is made by a mechanism which compares the current duration values with those in working or reference memory to decide on the adequate temporal response (decision system). Thus, the timing basic system in this model consists of three separable stages: the clock stage, the memory stage, and the decision stage (Allman & Meck, 2012; Block, 1990; Coull et al., 2011; Teixeira et al., 2013).

PD patients are considered to have a slow internal clock (pulses are stored at a slow rate), particularly when OFF-medication (Lange et al., 1995; Pastor et al., 1992). In this case, if the internal clock runs at a slower pace than objective time, verbal underestimation and over-reproduction of time are expected (Pastor et al., 1992). Pastor et al. (1992) confirmed this assumption by finding that PD patients underestimated the duration of a time interval in the verbal temporal estimation and over-reproduced the time interval when compared to the CG.

Another aspect observed was that change occurring at each stage of temporal processing result in specific patterns of accuracy and variability in the time perception when the scalar property is taken into account. The scalar property considers the positive correlation between the standard deviation of an estimated interval and the mean interval length, which keeps the coefficient of variation stable across different intervals (Gibbon, 1977). However, when it is request temporal reproduction, PD patients tend to violate the scalar property due to alterations in internal clock speed. In the study by Jones et al. (2008), in which PD patients performed a task of temporal judgment, adherence to the scalar property was observe in the time production method. But, in the temporal reproduction task the scalar property was violate independently of whether PD patients were medicated.

While in the study by Jones et al. (2008) the PD patients medication status did not appear to affect the internal clock speed and, consequently, temporal reproduction, other studies point in another direction (Koch, Brusa et al., 2004; Koch, Oliveri et al., 2004; Malapani et al., 1998; Malapani et al., 2002) and show the influence of dopamine on the scalar property. Malapani et al. (1998) and Malapani et al. (2002) found a normal reproduction of time for PD patients in the ON drug state; by the other side, they verified a violation of the scalar property by PD patients tested OFF medication. In the study by Koch, Brusa et al. (2004), PD patients without treatment (OFF deep brain stimulation and OFF medication therapy) showed overestimation of time interval, violating the scalar property, in which it was expect underestimation. These findings (Koch, Brusa et al., 2004; Malapani et al., 1998; Malapani et al., 2002;) indicate that maintenance of the scalar property is related to dopaminergic treatment. In this sense, studies have shown that slow internal clock in PD patients may be speeded up by L-Dopa (Perbal et al., 2005) and slowed down by dopamine antagonists (Rammsayer & Classen, 1997).

Another stage that seems to be influence by drug state is the memory stage (Malapani et al., 1998; Malapani et al., 2002). Malapani et al. (1998) and Malapani et al. (2002) observed that PD patients in the drug-OFF state reproduced two different intervals by over reproducing the short interval (5s) and under reproducing the long interval (21s). The authors denominated this finding as ‘migration effect,’ where there is a migration of intervals time toward each other. In this phenomenon, the authors noticed a non-scalar variability evidenced when it was present two-time memories, and they must be remembered. According to authors the ‘migration effect’ would be due to mnemonic processes and not to the effect related to the clock phase or the decision process. Consequently, there would be dissociation between temporal memory deficits and changes in clock speed in PD patients.

Also, the SET model links timing processes to brain structures (Jones et al., 2008; Koch, Oliveri et al., 2004; Koch et al., 2005; Malapani et al., 1998; Wearden et al., 2009;). Distinct parts of the timing system were mapped in the brain, and it was observed that the substantia nigra pars compacta (SNPC) play a time-keeping role, being responsible for providing the pacemaker with input to the striatal structures, which would connect to the prefrontal areas, which would be essentially responsible for decision-making processes (Meck, 1996). Studies conducted by Harrington et al., (1998) and Harrington et al. (2011), investigated the neurobiology of time perception, and pointed out the basal ganglia and their thalamus-cortical connections involved in timing operations. The authors also found that the impairment of time judgment in PD patients appears to originate from nigrostriatal and mesocortical dysfunction in systems that mediate temporal and non-temporal control processes.

A model that seems to advance the assumptions of the SET model is T*he Striatal Beat Frequency Model* (SBF) (Buhusi & Meck, 2005; Coull et al., 2011; Matell et al., 2003; Matell & Meck, 2000, 2004; Meck et al., 2008). The SBF model defends that time interval processing depends on detecting coincident neuronal oscillations in subcortical and cortical interations. For this, BG neurons would detect specific oscillatory activation patterns of frontal cortical areas during time encoding in working memory. This occurs as follows: at the onset of a signal to-be-timed, cortical, and thalamic neurons reset, synchronize, and begin to oscillate in their endogenous periodicities. Then, they would send signals to striatal neurons that would trigger action potentials (pulse of dopamine), thus strengthening the synapses in the striatum, favoring the recording of the duration in memory. After, neurons in the striatum would compare the current pattern of activations with a firing pattern previously stored in memory. When neural computation is over, the striatum would send a signal to other regions of basal ganglia, which in turn would send signals back to the cortex through the thalamus, and the time estimation is computed (Allman & Meck, 2012; Matell & Meck, 2004). Wojtecki et al. (2011) studied the subthalamic nucleus (STN) pathways and the SBF model, investigating the influence of DBS in the STN at different stimulation frequencies on the temporal judgments of PD patients. The authors considered that the STN-DBS differentially modulates motor and non-motor functions depending on the frequency of stimulation, probably because it affects the subcortical-cortical oscillatory loops (Timmermann et al., 2004; Wojtecki et al., 2011).

Yet another model is the *Attentional-gate Model* (Hicks et al., 1976; Thomas & Weaver, 1975; Zakay, 1989; Zakay & Block, 1996). This model adds attention processes to the temporal information processing. In brief, the less attention is allocated to the temporal task (because it is share with a non-temporal task), the fewer pulses are account for by the accumulator. A smaller number of accumulated pulses lead to a shorter temporal reproduction than the objective time.

Studies using the dual-task paradigms, in which one must pay attention to time while performing another task, found that PD patients experienced durations as shorter than control participants. This finding was attribute to fewer pulses being accumulate and transferred to memory (Block & Zakay, 1997; Perbal et al., 2005).

Likewise, the decision-making stage also seems to be affected by attentional processes, since it is in this stage that it is determined when the current duration is sufficiently close to the duration stored in long-term memory (Harrington & Haaland, 1999). Riesen and Schnider (2001) suggested that attention deficits present in PD patients would affect their time judgment. They observed that medicated PD patients made more errors than controls in discriminating short durations. The deficit in dividing attention between a temporal task and another non-temporal task would explain the difficulties in discriminating the durations. Perbal et al. (2005) evaluated the relationships between internal clock rate, cognitive functions, and time estimation in PD patients in the dual-task paradigm, in which attention was divided between estimating time and simultaneously performing a reading. The results showed a tendency for PD patients to reproduce more variable durations than CG. Thus, in dual tasks, PD patients tend to focus on one task, paying less attention to another task to be perform (Bialystok et al., 2008).

In general, in each of the models mentioned above, it is assumed that cognitive processes would be directly involved in the time perception and attentional and memory components show to be involved in the processing of temporal information. However, it is known that more models have been develop, such as studies on the SBF that have advanced, and been integrate into the cognitive architecture of the *Adaptive Rational-Thought Control* (ACT-R) as dedicated timing modules that are able to make use of from memory. and decision-making mechanisms contained in the ACT-R (see van Rijn et al., 2014, for more). Also, mathematical modeling has been a useful tool for understanding the neurodynamical and computational mechanisms of cognitive abilities like time perception, and for linking neurophysiology to psychology (see Hass & Durstewitz, 2014, for more).

Cognitive processes in the time perception: memory and attention

Cognitive processes such as memory and attention appear in studies as inextricably linked to temporal information processing (Fontes et al., 2016; Honma et al., 2016; Jones et al., 2008; Koch, Brusa et al., 2004; Magalhães et al., 2018; Perbal-Hatif, 2012; Pouthas & Perbal, 2004; Teixeira et al., 2013; Wearden et al., 2008). PD patients are known to have deficits in different cognitive functions (Schapira et al., 2017; Sveinbjornsdottir, 2016; Tarakad & Jankovic, 2017). Thus, studies on time estimation in PD patients have suggested that impaired duration judgments would be related to either memory deficits or to reduced attention (Dušek et al., 2012; Honma et al., 2018; Koch et al., 2005; Koch et al., 2008; Koch, Brusa, et al., 2004; Malapani et al., 1998; Malapani et al., 2002; Motta et al., 2019; Pastor et al., 1992; Perbal et al., 2005; Riesen & Schnider, 2001; Torta et al., 2010; Wojtecki et al., 2011).

In this sense, PD patients show deficits in temporal perception in a dual-task context (Motta et al., 2019; Torta et al., 2010; Riesen & Schnider, 2001). This is because PD patients tend to turn their attention to one of the tasks and lose focus on the other (Torta et al., 2010). Riesen and Schnider (2001) conducted a study in which, at first, PD patients performed the temporal discrimination of two temporally overlapping intervals. The task consisted of presenting a rectangle on a screen, followed by the presentation of another rectangle, both shapes changed color over time, and participants should indicate which shape had remained with a certain color for the longest time. Durations ranged from milliseconds to few seconds. In a second moment, during time intervals of 12s, 24s and 48s, patients had to press a key at a rate of 1 Hz per second, while reading random numbers. Afterwards, they verbally estimated the task duration. The results found showed that PD patients presented impairment in temporal discrimination. According to the authors, this finding was due to a disorder in the patients' ability to divide attention, i.e., failure to maintain attention to one stimulus while the other appeared or disappeared from the screen. On the other hand, the PD patients were as accurate as the controls in the verbal estimation of intervals of up to 48s. The authors argue that this result shows that attention would be focus only on the passage of time and would not be affect by the proposed visual-motor task. In study by Motta et al. (2019), no differences were found between the verbal temporal estimation of PD patients and controls in a task which participants judged the time they spent manipulating artworks. However, the authors pointed out that, despite the absence of statistical difference, the PD patients showed less overestimation of the task duration than the control participants. The findings of these studies (Motta et al., 2019; Riesen & Schnider, 2001) seem to indicate that in tasks involving motor action in a dual-task proposal, the verbal temporal estimation of PD patients would show no changes when compared to control participants.

Besides, alterations in PD patients time estimation were observe in temporal reproduction in dual-task context. Torta et al. (2010) verified that PD patients showed impairment in the reproduction of the duration of their motor actions but did not showed alterations in the time interval reproduction. However, it is important to emphasize that the last task consisted of paying attention to the time interval and only after reproducing it; therefore, it can be assumed as a single task, thus, requiring less of the load cognitive. Considering the results presented by the studies (Motta et al., 2019; Riesen & Schnider, 2001; Torta et al., 2010), it would be possible to assume that PD patients would present fail in duration reproduction and in temporal discrimination when performing dual task, but not in verbal temporal estimation. In this sense, dysfunctions in PD patients' divided attention would be evidence in temporal reproduction involving motor activity (Torta et al., 2010) and in time discrimination of visual stimuli presentation (Riesen & Schnider, 2001) in a dual-task context. Results found by Perbal et al. (2005) seem to go in the opposite direction the assumption of the effect of motor activity in a dual-task context on the temporal reproduction of PD patients. The proposal was that PD patients performed a duration reproduction task, in which they should evaluate the display duration (5s, 14s, or 38s) of visual stimuli while reading aloud digits that appeared on the screen during the presentation The results showed that the temporal reproduction did not differ between PD patients and controls. Both groups under-reproduced all the three target durations. Performances were related to memory test scores, showing that shorter time reproduction correlated with the lower scores for delayed recall. These results seem to point not only to the influence of attention capacity on the time perception, but also to the involvement of the memory processes in temporal judgment.

Memory effects on the duration’s perception of PD patients have been found in several studies (Dušek et al., 2012; Honma et al., 2018; Koch et al., 2005; Koch et al., 2008; Koch, Brusa, et al., 2004; Malapani et al., 1998; Malapani et al., 2002; Wojtecki et al., 2011). Among researchers, the study by Malapani et al. (1998) and Malapani et al. (2002) drew attention to a specific phenomenon related to memory and temporal perception. In these studies, PD patients were asked to reproduce durations of presentations of visual stimuli (8s and 21s) in the OFF and ON condition of medication. The findings showed that when using medication, PD patients were accurate in the temporal reproduction of the two durations. On the other hand, when PD patients were OFF medication, a distortion in accuracy was observe for both durations. The 8s interval was reproduced longer and the 21s interval was reproduced shorter than they actually were. This phenomenon was call *migration effect*. However, in a second trial, in which patients reproduced only one duration (21s), it was observed that PD patients OFF medicine over reproduced the time interval (Malapani et al., 1998). After, another experimental design was applied, in which PD patients in On and OFF medication performed the temporal reproduction task in two days (Malapani et al., 2002). On the first day (coding phase), the patients were train in a short (6s) and long (17s) interval. On the following day (decoding phase), the participants were asked to reproduce the time intervals trained on the previous day. Patients were distributing into distinct groups to perform the task each day in different drug states (ON-ON; ON-OFF; OFF-ON; and OFF-OFF). The results showed that, regardless of the task phase (encoding and decoding), whenever patients were in the OFF-drug state, the migration effect was observed. The authors (Malapani et al., 1998; Malapani et al., 2002) concluded that when PD patients in OFF medication are asked to remember two durations, the memory of a previously learned interval seems to affect the estimation of an interval learned later. Thus, driving the migration from one duration to another. This distortion of the perception of time observed in PD patients was attribute, by the authors, the dysfunction of temporal memory retrieval, which would be sensitive to treatment with dopaminergic agents.

Other studies also found migration effect on the temporal reproduction of PD patients (Dušek et al., 2012; Jones et al., 2008; Koch et al., 2005; Koch et al., 2008; Koch, Brusa, et al., 2004; Wojtecki et al., 2011). The findings showed that the precuneus would be involved time judgment task. it is a brain region related to episodic memory retrieval (Dušek et al., 2012); patients in OFF STN-DBS and OFF medication also exhibited migration effect (Koch, Brusa, et al., 2004), and evidence indicates that the frequency of subthalamic DBS stimulation may interfere with temporal information processing (Wojtecki et al., 2011). These results indicate that DBS would have similar effect to treatment with dopamine on the time perception in PD patients.

In addition, the migration effect was present in the temporal reproduction of patients with left hemi-PD in OFF therapy, indicating that the basal ganglia of the right cerebral hemisphere would be critical in subserving the recovery process of time intervals (Koch et al., 2005). Furthermore, the migration effect appeared when PD patients OFF medication performed the temporal reproduction of supra-second durations, but not for millisecond intervals (Jones et al., 2008; Kock et al., 2008). This suggests that the 'migration effect' would be a phenomenon that occurs only in the supra-second interval, which points to a dissociation between cognitive processes involved in the perception of different time intervals, particularly in the range of milliseconds to seconds (Malapani et al., 2002).

The components of attention and memory shown to be part of the processing of temporal information. When these factors do not work as expected, the time perception is impaired. Particularly, as PD patients present cognitive disorders, their perceptions of events durations are altered, which can lead to impairment of the functionality and of the task management. Therefore, the PD patients unable to accurately estimate the time of an event, can lose control of the duration of their movements, the exact moment to act upon a situation, and subjectively perceive the time of an event as longer or shorter, which could compromise your experience of that moment, making it less interesting or pleasurable. In addition, the PD patients would have difficulty perceiving and managing time in a dual-task context, such as cutting one food while managing the cooking of another.

Time Perception and Motor Activity

PD is characterized by motor symptoms, including resting tremor, bradykinesia, and rigidity of movement. These symptoms arise primarily as result of decreased dopaminergic network due to degeneration of dopamine neurons in the BG. Consequently, PD patients have difficulty initiating movement, and once initiated, movement is slow and may be difficult to stop (Pagonabarraga et al., 2021). Considering these aspects, studies indicate that the abnormal motor action in PD patients may reflect an impaired temporal judgment (Wearden et al., 2008; Pastor et al., 1992).

In this sense, the internal counting of time appears as a motor action present in the subvocalization during counting. PD patients would show a slower internal count through subvocalization, which would have repercussions on the time estimation (Pastor et al., 1992). Similarly, when the internal count appears associated with a finger or hand tapping task, another motor action, PD patients have their temporal perception altered (Honma et al., 2016). Furthermore, when patients are asked to count aloud while performing a tapping task, impaired temporal reproduction was observed, regardless of whether the patient is in an OFF- or On-therapy condition (Kock et al., 2005). These results suggest that the dysfunction of the time perception observed in PD patients would be related to motor aspects implicates in task performance (Pastor et al., 1992; Wearden et al., 2008).

Also, this assumption was applied to the temporal reproduction method (Perbal et al., 2005; Wearden et al., 2008). In general, in this method to register the duration, a button is press once to mark the beginning of the reproduction and pressed again to register the end. Therefore, a motor action is performed, which is known to be impaired in PD patients. In this sense, the method used to collect the duration judgment would be affect by motor aspects, such as bradykinesia (Pastor et al., 1992; Perbal et al., 2005; Wearden et al., 2008). Investigations of PD patients' reaction time showed that they tend to initiate and execute movements more slowly, which would contribute to inaccuracy of the judgment of durations (Honma et al., 2016; Pastor et al., 1992). According to Wearden et al. (2008), in studies on temporal estimation, the use of manual responses or tasks in which the counting of time is probably involved is very frequent, and it is rare not to use the manual function.

However, this hypothesis of the relationship between abnormality in time perception and motor deficits does not seem to hold up when studies show that PD patients were as accurate as participants without PD in estimating durations in a number reading aloud task associated with tapping; and both participants without and with PD have been shown to be able to maintain a constant rhythm of taps over time intervals (Riesen & Schnider, 2001). Likewise, Jones et al. (2008) found no differences between the performance of controls and PD patients in temporal reproduction and response time of a motor task; and the reaction time of patients did not seem to be less effective than in people without PD. Therefore, the contradictions found in the results of the studies seem to indicate the weakness of the assumption that alterations in PD patients motor activity would be "responsible" for impairment of time perception.

Moreover, a study evaluated the ability of PD patients to estimate the duration of their motor acts and estimate the duration of time intervals. The results show that PD patients showed impairment in reproducing the duration of their motor actions, while accurately reproducing the duration of time intervals. In this study, the participants were requested to perform two tasks. First task, they should judge the duration of their own motor performance. The task was unscrewing a stud nut for the entire length. After the task, they should reproduce the time interval they had employed to accomplish the task. In the second task, the examiner tapped twice on the desk to produce a target time interval that should be reproduce by the participant. The time interval was the same that the participant had previously used to unscrew the bolt. The findings showed that, in the first task, untreated PD patients under-reproduced the duration of their actions. By contrast, in the second task, they precisely reproduced the duration of the time interval. According to authors, the results found indicate that in PD patients the ability to reproduce motor acts may be dissociate from the ability to reproduce time intervals. Similarly, Motta et al. (2019) examined the perception of time in PD patients using a motor activity. The participants were asked to manipulate artworks, and immediately after, verbally estimate the duration of their manipulations. The results showed that PD patients overestimated the time spent manipulating artwork. The authors argue that the complexity of the motor task associated with the difficulty of executing a motor plan may explain the distortion observed in the time perception of PD patients.

However, before considering that any motor activity would affect the time perception, it is important to consider that there are studies that did not use motor tasks and showed alterations in temporal judgment in PD patients (Riesen & Schnider, 2001; Wearden et al., 2008). Regarding the time reproduction method through motor response, studies that used this method found alterations in reproduction in PD patients (Dušek et al., 2012; Malapani et al., 1998; Malapani et al., 2002; Pastor et al., 1992; Wojtecki et al., 2011); and studies that used this method found no alterations in temporal reproduction (Honma et al., 2018; Jones et al., 2008; Torta et al., 2010). This way, other factors, beyond the motor action, must be taking in account when abnormal time perception is observed in the temporal judgment where a motor task is present.

Neurobiological and neurochemical structures: temporal information processing

Considering neurobiological and neurochemical aspects involved in the time perception, structures such as the BG and the dopaminergic system appear as critical for the temporal information processing (Dušek et al., 2012; Koch et al., 2005; Koch et al., 2008; Koch, Brusa et al., 2004; Malapani et al., 1998; Malapani et al., 2002; Perbal et al., 2005; Torta et al., 2010; Wearden et al., 2009; Wojtecki et al., 2011).

Studies showed that, specifically, the GB, in the right hemisphere, plays a significant role in the time perception. This is because, it was observed that patients with left hemi-PD presented impairment of temporal reproduction when in OFF medication, highlighting the importance of these structures and pointing out the influence of the dopaminergic system on temporal perception (Koch et al., 2005).

However, evidence suggests that BG would play a role in modulating durations in the range of seconds, but not in millisecond intervals (Koch et al., 2008). Koch et al. (2005) conducted a study in which PD patients showed impairment in the reproduction of supra-second durations, but not in the reproduction of millisecond intervals. According to the authors, the result suggests that other brain structures can provide a representation of time in the millisecond range, regardless of the BG activity. Similarly, Wojtecki et al. (2011) observed that bilateral stimulation via STN-DBS improved PD patients’ performance in reproduction and temporal production of intervals of seconds (15s). On the other hand, the temporal discrimination of millisecond intervals (800ms to 1600ms) of PD patients with STN-DBS was like that of controls regardless of the level of stimulation. The findings underline that deficit in the BG function are mitigate by the DBS for estimating the second interval, but the BG would not be involved in processing short intervals in the millisecond range. However, the authors warned that their results show that the duration of milliseconds would be less vulnerable to electrical stimulation of the STN, but that it is neither prove nor discard the involvement of the BG in the estimation of short time intervals. In this direction, another study (Jones et al., 2008) referred that the integrity of the BG is important for the temporal processing of millisecond and seconds ranges. PD patients overestimated the production of intervals between 30s and 120s compared to controls and had a worse percentage of target deviation when ON medication than OFF medication. For the reproduction range of milliseconds (250ms–2000ms), it was found under reproduction of the interval of 2000ms, and greater target deviation and variability for the duration of 250ms. The results suggest that BG act both in durations of seconds and in durations of milliseconds. As for dopamine not having improved performance on tasks, a "dopamine overdose," would have contributed to the result. This is because the areas of the BG with the lowest dopamine levels would have benefit from drug therapy, and parts with less dopaminergic depletion would have suffered from an "overdose" with levodopa therapy, thus, affecting the time perception.

Furthermore, studies suggest that the BG and the frontal-striatal circuits would be involved in the time perception (Koch et al., 2005; Koch, Oliveri et al., 2004; Torta et al., 2010). The pathology in GB could induce dorsolateral prefrontal cortex dysfunction (DLPFC), a target area for mesocortical dopaminergic system output projections (Koch et al., 2005). In the study conducted by Koch, Oliveri et al. (2004) rTMS in the right DLPFC improved time reproduction in PD patients. Besides, STN-DBS patients ameliorated their abnormal performance on a temporal reproduction task when on On-stimulation and On-medication (Koch, Oliveri et al., 2004). These data indicates that the mesocortical circuit involving the BG and the DLPFC can constitute the neural network subservient to the time perception, and that the STN stimulation can improve decision-making processes for the duration estimation, facilitating thalamus-cortical projections for DLPFC (Koch, Brusa et al., 2004; Koch, Oliveri et al., 2004). Particularly, the precuneus was point out as a cortical portion connected to the temporal judgment (Dušek et al., 2012). The brain activity of this structure was present in DP patients in OFF medication during the time coding phase, but during the decoding phase (temporal reproduction), bilateral deactivation of the precuneus occurred. On the other hand, the same activation pattern was not observed when reproducing the time in ON medication. Based on these findings, dopaminergic transmission may increase or decrease precuneus activity during a time interval judgment. (Dušek et al., 2012).

The dopamine appears as fundamental in the processing of temporal information, especially when studies show that PD patients under the effect of dopaminergic treatment present a significant improvement in the performance of temporal tasks (Koch et al., 2005; Koch et al., 2008; Koch, Brusa et al., 2004, Malapani et al., 1998, Motta et al., 2019; Pastor et al., 1992, Perbal et al., 2005, Riesen & Schnider, 2001, Wearden et al., 2008, Wearden et al., 2009,). Dopaminergic medication appears to “normalize” the pattern of dysfunctional neuronal activity during processing of temporal information in PD patients. Studies such as one by Malapani et al. (1998) and Malapani et al. (2002) found accurate time reproduction in PD patients in the ON medication state, and impaired temporal reproductions when the patients were in OFF medication. There is also evidence that dopamine may allow compensatory activation in the cortical region, which would reflect a more accurate time perception (Dušek et al., 2012).

Furthermore, PD patients in dopaminergic treatment showed improved cognitive performance in temporal judgment tasks. Perbal, et al. (2005) observed that time reproduction did not differ between PD patients in ON medication and controls and suggested that dopamine may have beneficial effects on the memory functions involved in temporal judgments. Comparable results were found by other studies (Malapani et al., 1998; Malapani et al., 2002; Riesen & Schnider, 2001).

On the other hand, there are mixed results on the effect of dopamine on the perception of intervals of seconds and milliseconds. While studies showed that PD patients in ON medication showed alteration in temporal reproduction for durations of milliseconds, but not for reproductions of seconds (Honma et al., 2016), other studies found that PD patients with dopamine supplementation showed accurate reproduction for millisecond intervals and impaired reproduction for supra-second intervals (Kock et al., 2008). The hypothesis is that non-dopaminergic neurotransmission such as cholinergic, noradrenergic, and serotonergic systems may play a role in modulating time perception in PD patients, thus mitigating the effects of depletion of dopaminergic neurons in modulating temporal information processing (Kock et al., 2008). Also, Wearden et al. (2009) found that PD patients' performance on the temporal judgment task was not affect by the medication status (OFF or ON levodopa). They conducted a study in which PD patients verbally estimated the duration of short 500 Hz tones (325ms–1,225ms) in trials in which the tone was preceded by 3s of 5 Hz clicks (10ms long 500 Hz tones, spaced 190ms apart), or displayed without clicks. The result showed that there was a significant effect of clicks and duration of stimuli, but there was no effect of medication.

Thus, there would is the possibility of context dependence for the effects of dopamine in the temporal judgment of PD patients. Contradictions among the results can be explain by the fact that, although dopamine replacement improves motor symptoms in PD patients, it does not restore the functioning of the nigrostriatal and mesocortical systems, which are vital for temporal processing (Harrington et al., 2011; Meck, 2006). Furthermore, the heterogeneity in PD, and consequently the individual variability of the responsiveness of the various neural networks to dopamine replacement therapy, may justify the different results (Merchant et al., 2008).

In this review, temporal reproduction and verbal temporal estimation of PD patients were examine. An intricate association of factors seems to be involved in the perception of the duration of an event: cognitive processes, motor function, neural structures, brain systems and neurochemical transmissions. This shows how the processing of temporal information takes place through a wide web of interactions. In PD, the motor and cognitive impairment, associated with the degeneration of the dopaminergic system, directly influences the dysfunctions in the time perception observed in this population.

This review sought to analyze the different results, to integrate existing knowledge, and showed that the studies present a mixture of results and even contradictions on the subject. A way out of this, would be to explore the heterogeneity of PD: clinical subtypes with predominant symptoms (e.g., akinetic-rigid or tremor), age at onset, disease duration and stage, and presence of motor and non-motor symptoms. Greater attention to clinical and experimental subtypes could contribute to clarifying the diversity of results (Merchant et al., 2008). Cluster analyses could be use.

However, despite the mix of results, some points can be highlighted: (a) the evidence of motor dysfunction and of the time perception in DP patients, confirming the important role of BG for these functions, (b) and consequently the treatment with dopaminergic medication and STN-DBS as having the potential to modulate performance in temporal judgment tasks; (c) the perception of time is altered both for time ranges in milliseconds and for seconds; (d) and predominate influence of the SET model on theoretical aspects. The improvement of models on temporal behavior would contribute to broaden and assign new angles of view to advances in research on temporal information processing.

Finally, it is known that the time perception is the subjective judgment of a perceived time interval, and movement is not included. The temporal reproduction method introduces a motor element, which can be a co-founder. However, although its involvement is a point of discussion, the motor aspect is often involved in the time perception process. From an ecological perspective, temporal perception occurs in a moving world in which the person is in constant movement. It is recommended that both methods of judging durations (temporal reproduction and verbal time estimation) can be integrated into methodologies that consider approaching tasks performed in everyday life. This could broaden the understanding of the time perception process.

This review is an excerpt from the literature on the time perception in PD patients. The studies presented here were the result of research that used keywords; therefore, other studies were and have been developing on the subject. However, the objective of this review was not to exhaust the topic, but to synthesize significant factors in this field. Much still needs to be discover and understood, new research will expand and improve knowledge about the time perception in PD patients.

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3 Immediate effects of auditory stimuli on upper limb movement in patients with Parkinsons's disease: A systematic review

Many studies have documented the use of external cue to improve the motor activity in human (Forte & De Vito., 2021; Gonzalez-Hoelling et al., 2012; Thaut et al., 2015; Wu, et al., 2020). External signal, such as visual markers or auditory stimulation, have been using to facilitate serial movements. Compared to the visual stimuli, auditory stimuli have been showing to yield shorter reaction time (Nombela et al., 2013; Shelton & Kumar, 2010). In particular, rhythmic auditory stimulation (RAS) has been a powerful means to enhance motor performance (Forte & De Vito., 2021; Thaut et al., 2015). In this respect, diverse ways to provide the RAS are used, such as metronome and music (Nowak et al., 2006; Rose et al., 2019; Sabaté et al., 2008; Sacrey et al., 2009; Sacrey et al., 2011). Likewise, different frequencies of RAS have been testing (Freeman et al., 1993; Heida et al., 2014; Rose et al., 2019; Sabaté et al., 2008). The results of studies have indicated that health individuals (Nascimento et al., 2020) and people with different neurological illnesses (Forte & De Vito., 2021; Gonzalez-Hoelling et al., 2012; Shahraki et al., 2017) have benefited from sound stimuli. This is the case of people with Parkinson's disease (PD patients. Forte & De Vito., 2021). Studies show that treatment program based on RAS ameliorate the motor action in this population (Erra, et al., 2019; Koshimori & Thaut, 2018; Ma et al., 2004; Nishida, et al., 2021).

The effect of RAS relies on the innate human capacity to extract rhythm from the external world (Ashoori et al., 2015; Erra et al., 2019), and on a mechanism called *entrainment*, which is defined as the process of coupling between systems, which can lead to synchronization (Buard et al., 2019; Janzen et al., 2019; Nombela et al., 2013; Rose et al., 2019). This occurs when the timing of movement is aligned simultaneously to a specific point with the pacing source (Rose et al., 2019).

The neural basis of entrainment has been explaining by connections between auditory system and motor system. RAS would generate a firing rate that entrains the firing rate of the motor system, producing synchronization of motor activity with beats of the sound cue. This mechanism has the potential to bypass dysfunctional basal ganglia (BG) in PD patients (Braunlich et al., 2019; Janzen et al., 2019; Thaut et al., 2015).

It is known that PD is consequence of depletion of doparminergic neurons in the BG, which participates in the movement control by internally generated cues (Fox et al., 2018; Jones & Jahanshahi, 2014). In general, the following cardinal symptoms are present in PD patients: rest tremor, bradykinesia, muscle rigidity and postural instability. However, when the RAS is provides, it constitutes as an external cue that compensate the deficit in the BG connections, which can result in improvement of motor symptoms (Heida et al., 2014; Nowak et al., 2006).

In the present study we will focus on the immediate effect of auditory stimuli on upper limb movement in PD patients. Although auditory stimuli have primarily be use for gait improvement, it is possible extend their use to other movements (Braunlich et al., 2019; Nombela et al., 2013). For example, arm and finger movements (Freeman et al., 1993; Horin et al., 2020; Vercruysse et al., 2012). Besides that, consider the immediate effect of single auditory cue or successive auditory cues on movement can contribute to clarify common features that could influence on studies results (Ma et al., 2004). Thus, the primary aim of this review was to summarize the current state of knowledge on the immediate effects of auditory stimuli in improving arm motor performance of PD patients. Specifically, we aimed to: (a) describe the types of the auditory stimuli used; (b) the methods of upper limb motor activities used; (c) summarize the evidence regarding the efficacy of each type of auditory stimuli; and (d) highlight the cognitive components and the neural system associated with auditory stimuli and movement in PD patients.

3.1 Methods

Search Strategy

A detailed literature search, aided by computer, until February 2021, was conduct by accessing the following two electronic databases: PubMed and Web of Science. ‘Parkinson disease’ was used as a major concept search term and it was combined with ‘auditory stimuli’, ‘music’ and ‘rhythmic auditory stimulation’. Furthermore, the reference lists of the selected articles were scan for relevant additional literature.

Inclusion criteria

Studies were included in the review if they fulfilled the following criteria: (a) external sensory cue (i.e., auditory) was used as part of the procedure; (b) studies that showed an immediate effect of the auditory stimulus; (c) the interventions were implemented with PD patients (both sexes, all ages and any disease duration); (d) superior limb movement was used as a functional outcome measure. There was no period. If the study did not evaluate the superior limb activity, it was automatically excluded. In addition, articles on controlled trials, animal studies, conference proceedings, reviews and non-English publications were excluded.

Study selection, data extraction and analysis

Initially, articles were select by title. Where the title did not provide sufficient detail to determine study inclusion, the abstract was examined and, if it appeared relevant, the full text content was downloaded and analyzed. Studies that met the inclusion criteria were read in full. Also, reference lists of identified articles were search for further studies. Selected studies were compared to remove duplicate records. The first author (MRM) analyzed these data. Then, the second author (JLOB) analyzed the data and, if there was any divergence about inclusion of the article, it was discussed between the two reviewers and, if necessary, the opinion of the third author (VT) was requested.

In total, 153 articles were identified. Of these 17 studies were included in this review. The following data were extract from the selected studies: descriptive characteristics of PD patients, motor activity and auditory stimulus used, experimental method used, main results found, cognitive component involved in motor action in the presence of auditory stimulus, and motor and neural systems involved in motor activity and auditory stimulus relationship. The analysis method planned for this review was the descriptive synthesis.

3.2 Results

A total of 153 articles evaluating auditory stimuli and movement in PD patients were identified: PubMed (*n*=54) and Web of Science (*n*=99) databases (Figure 1). The reference lists of articles were explored manually, and three additional articles were identified. Duplicates were removed (*n*=82) and 31 articles were assessed for eligibility after excluding 40 articles during the screening process. A total of 17 studies fulfilled the selection criteria and were included to be entire analyzed (Braunlich et al., 2019; Buard et al., 2019; Fernandez-Del-Olmo et al., 2013; Freeman et al., 1993; Gueye et al., 1998; Heida et al., 2014; Horin et al., 2020; Janzen et al., 2019; Ma et al., 2004; Ma et al., 2009; Nowak et al., 2006; Rose et al., 2019; Sabaté et al., 2008; Sacrey et al., 2009; Sacrey et al., 2011; Vercruysse et al., 2012; Wu et al., 2020). Figure 1 shows the flow diagram summarizing the selection process.

Figure 1

Flowchart of study selection process

Identification	153 studies identified though PubMed and Web of Science database	3 additional studies identified though the reference lists
	111 studies selected by title	45 studies removed
	71 studies after duplicates removed	40 studies excluded
Screening	71 studies screened	
	45 studies selected by abstract	26 studies excluded
Eligibility	31 full text studies assessed for eligibility	14 studies excluded
Included	17 full text studies included in the qualitative synthesis	

The results of this review were presented in six sections in order to provide a comprehensive methodological overview. The order was present as such: (a) descriptive characteristics of the studies and participants, (b) the auditory stimuli, (c) the upper limb motor tasks, (d) the functional outcomes, (e) the cognitive component involved and (f) the neural system associated with auditory stimuli and movement in PD patients. Also, a comprehensive list of investigations into auditory stimuli in PD patients is provide in Table 1.

Descriptive characteristics of the studies and participants

The combined sample size of the seventeen studies was 294 PD patients; 122 were female and 156 were male. One study did not have women as participants (Ma et al., 2004) and another did not mention the gender of the sample (Sabaté, et al., 2008).

Nine studies used the mean of the Hoehn and Yahr Scale to present the stage of disease (Fernandez-Del-Olmo et al., 2013; Horin et al., 2020; Janzen et al., 2019; Rose et al., 2019; Sabaté et al., 2008; Sacrey et al., 2009; Sacrey et al., 2011; Vercruysse et al., 2012; Wu et al., 2020), three studies showed only the minimum and maximum stage (Gueye et al., 1998; Ma et al., 2004; Ma et al., 2009), and in five studies, the stage of the disease was not found (Braunlich et al., 2019; Buard et al., 2019; Freeman et al., 1993; Heida et al., 2014; Nowak et al., 2006).

Two studies used the Unified Parkinson's Disease Rating Scale (UPDRS) to identify the level of disease (Sabaté et al., 2008; Wu et al., 2020), and seven papers used only part III (motor) of this scale (Fernandez-Del-Olmo et al., 2013; Horin et al., 2020; Janzen et al., 2019; Nowak et al., 2006; Rose et al., 2019; Sacrey et al., 2011; Vercruysse et al., 2012).

The mean duration of the disease was cited by ten studies (Fernandez-Del-Olmo et al., 2013; Freeman et al., 1993; Gueye et al., 1998; Horin et al., 2020; Janzen et al., 2019; Ma et al., 2009; Nowak et al., 2006; Rose et al., 2019; Vercruysse et al., 2012; Wu et al., 2020), three articles presented only the minimum and maximum duration (Heida et al., 2014; Ma et al., 2004; Sabaté et al., 2008), and in four studies, the duration of disease was not found (Braunlich et al., 2019; Buard et al., 2019; Sacrey et al., 2009; Sacrey et al., 2011).

Twelve studies mentioned that the tasks were performed during the ON dopaminergic medication status, that is, after intake the medication (Braunlich et al., 2019; Buard et al., 2019; Fernandez-Del-Olmo et al., 2013; Freeman et al., 1993; Gueye et al., 1998; Horin et al., 2020; Janzen et al., 2019; Ma et al., 2004; Ma et al., 2009; Rose et al., 2019; Sacrey et al., 2009; Wu et al., 2020); in two articles, the tasks were performed by the PD patients in the OFF (minimum of 12 hours without ingesting the drug) and ON status of the medication (Sabaté et al., 2008; Sacrey et al., 2011); in one paper, participants were on OFF medication when they performed the tasks (Vercruysse et al., 2012); and in two studies, the tasks were performed by patients with DBS (Deep Brain Stimulation. Heida et al., 2014; Nowak et al., 2006).

Finally, of the 17 studies included, fourteen of them had healthy participants as controls (Braunlich et al., 2019; Buard et al., 2019; Fernandez-Del-Olmo et al., 2013; Freeman et al., 1993; Gueye et al., 1998; Horin et al., 2020; Ma et al., 2004; Nowak et al., 2006; Rose et al., 2019; Sabaté et al., 2008; Sacrey et al., 2009; Sacrey et al., 2011; Vercruysse et al., 2012; Wu et al., 2020).

The upper limb motor activities

Across the 17 studies included five of them used index finger tapping task (Buard et al., 2019; Braunlich et al., 2019; Horin et al., 2020; Rose et al., 2019; Wu et al., 2020). One study proposed bimanual finger tapping (Vercruysse et al., 2012), and two studies used index finger tapping task plus rotary movement of the hand (Sabaté et al., 2008) and arm swing movement (Janzen et al., 2019). In another study, the tapping of the index finger was done through the flexion and extension movements of the wrist (Freeman et al., 1993). Five studies used the reach-to-grasp task: reach-to-write task (Ma et al., 2004), reach-to-lift task (Nowak et al., 2006), reach-to-transport task (Ma et al., 2009), and reach-to-eat task (Sacrey et al., 2009; Sacrey et al., 2011). Another three studies used a task of pointing a target with index finger (Gueye et al., 1998), flexing the wrist (Fernandez-Del-Olmo et al., 2013) and moving the hand between two dots (Heida et al., 2014).

The auditory stimuli

The types of auditory stimuli used, and the methods of administration showed be heterogeneous across the studies. Of the seventeen included studies, four examined the use of metronome and the frequencies were slow (0.5Hz-0.83Hz) and fast (2Hz-3.33Hz. Sabaté et al., 2008), between 1.6Hz e 4.8Hz for 10 to 16s (Heida et al., 2014), 1kHz, 85 dB for 60 s (Janzen et al., 2019); and 75ms beeps separated by breaks of 75ms (Nowak et al., 2006). Two studies used auditory pacing: a comfortable frequency for the participant or fast (i.e., 100% and 133% of the comfortable frequency. Vercruysse et al., 2012), and 300-400Hz for 16s (Braunlich et al., 2019). A study used music with a salient beat, but the frequency was not found (Horin et al., 2020) and two papers used music that was not embedded with RAS (Sacrey et al., 2009; Sacrey et al., 2011). A study analyzed the use of music with RAS and metronome for 30s: slow frequencies (1.15Hz-1.42Hz), medium frequencies (1.87Hz-2Hz) and fast frequencies (2.08Hz-2.4Hz. Rose et al, 2019), and other paper used 30s of music with RAS (1.6Hz-1.67Hz) and excerpts of weather forecast (Ma et al., 2009). A study used clicks of 1Hz to 5 Hz for 30s (Freeman et al., 1993) and other used a call bell (Ma et al., 2004). A study evaluated the use of warning signal, but the frequency was not found (Gueye et al., 1998), other used of auditory stimulus (30ms, 80dB) and startling auditory stimulus (30ms, 130dB), however the frequency was not found (Fernandez-Del-Olmo, 2013), and other paper used of acoustic burst stimuli (30ms, 2kHz, 70dB. Buard et al., 2019). A study investigated the use of RAS (50ms, 600Hz, 70dB) and visual cues (Wu et al., 2020). In addition, studies included in their analysis the exam of internally generated rhythmic cues (Braunlich et al., 2019; Horin et al., 2020; Ma et al., 2004; Nowak et al., 2006). And other papers verified the potential of auditory stimuli in entrain and synchronize the motor activity (Braunlich et al., 2019; Buard et al., 2019; Freeman et al., 1993; Heida et al., 2014; Janzen et al., 2019; Rose et al., 2019; Sabaté et al., 2008; Vercruysse et al., 2012; Wu et al., 2020).

Outcomes

Among the five studies that used music as an auditory cue, one study found a non-significant effect of music with RAS on the movement kinematic in a reach-to-transport task performed by PD patients in ON medication status (Ma et al., 2009). Two other studies that investigated the effect of music with RAS on the finger tapping task found that music improved movement entrainment and synchronization, however, made it more unstable compared to the metronome (Rose et al., 2019), and with higher movement variability compared to uncued condition (Horin et al., 2020). Two studies that used music without RAS found no improvement in the reach-to-eat task, regardless of the stage of the disease, i.e., mild, or advanced (Sacrey et al., 2009) or medication condition (Sacrey et al., 2011).

Among the four studies that used metronome: one observed greater peak rates of grip force and peak accelerations in the performance of PD patients in the OFF medication and OFF DBS condition in a reach-to-lift task in the presence of auditory cue (Nowak et al., 2006). Other study found that high frequencies (40, 120, and 200 beats/min) accelerated the rotary movement of the hand in PD patients regardless of the movement be real or imagined and of the medication condition (Sabaté et al., 2008). One study (Heida et al., 2014) observed that auditory cueing plus DBS improved the performance repetitive movement of hand by PD patients, regardless of the presence of the tremor, for the lowest (1.6 Hz) and highest (4.8 Hz) cueing frequency. The entrainment of tremor was observed at the highest frequency (4.8 Hz), and synchronization occurred in the absence of tremor with the 1.6 Hz cueing signal compared to 3.2 Hz. One study (Janzen et al., 2019) found that the finger tapping task showed a lower average inter-response interval, less difficulty in maintaining the tempo set by the metronome, and less response variability than the arm swing movement performed by PD patients in ON medication. The motor synchronization occurred more appropriately in the finger tapping task compared to the arm swing task.

Among the eight studies that used other types of auditory stimuli that were not music or metronomes, seven showed a significant effect of the auditory cue on PD patients motor activity in ON medication, as follows: one study (Gueye et al., 1998) found that PD patients showed shorter response time when auditory warning signs indicated the location of the target to-be-pointed. One study (Ma et al., 2004) observed that the PD patients benefited from the call bell comparison to the signal-absent condition in a reach-to-write task. Other study (Fernandez-Del-Olmo et al., 2013) found that the reaction time of the ballistic wrist flexion performed by PD patients decreased in the presence of auditory stimulus (750Hz, 80dB) comparison to a visual stimulus, and it was faster in the presence of startling auditory stimulus (750Hz, 130dB) than to the non-startle cue. One study (Freeman et al., 1993) found that PD patients were less stable than controls, tending to alter the speed of finger tapping produced by wrist movement according to clicks (frequencies 1, 2, 3, 4, and 5Hz): the lower frequencies generated acceleration of the movement and the higher frequencies led to the decline of the movement. In addition, in the absence of clicks, there was an increase in average tapping frequency and the rhythm became far more irregular. In another study (Vercruysse et al., 2012), more frequency error and variability of movement frequency were observed in the synchronization-continuation task of bimanual finger tapping performed by PD patients with Freezing of gait (FOG) in the absence of auditory pacing when compared to the PD patients without FOG and controls. One study (Braunlich et al., 2019) found a positive effect of simultaneous alternate auditory stimuli (300Hz and 400Hz) on finger tapping performed by PD patients: less tapping error and variability were note in the presence of sound than to the absence of the sound. Other study (Wu et al., 2020) found that the finger tapping movement of PD patients was more stable and tended to the synchronization in the presence of the RAS in comparison to visual stimuli for PD patients. At last, one study (Buard et al., 2019) did not find difference in the effect of the auditory cue on the finger tapping performed by PD patients. The stimulus used was an acoustic burst (2kHz, 70dB).

Cognitive component

Among the selected studies, attention appeared as a cognitive component involved in the processing and execution of motor action associated with auditory stimulus (Fernandez-Del-Olmo et al., 2013; Gueye et al., 1998; Horin et al., 2020; Ma et al., 2004; Ma et al., 2009; Nowak et al., 2006; Rose et al., 2019; Sacrey et al., 2009; Sacrey et al., 2011; Vercruysse et al., 2012).

A single external auditory cue was used as a strategy to draw attention and indicate the beginning of movement for PD patients showed facilitates the preparation and execution of the motor action (Gueye et al., 1998; Ma et al., 2004; Novak et al., 2006). Besides, it improved the kinematics of movement these patients (Nowak et al., 2006). Positive effects of this attention strategy were found both for simple and rhythmic movements, such as pointing a target with the index finger (Gueye et al., 1998), and for complex sequential movements such as grasp-to-reach (Ma et al., 2004; Novak et al., 2006).

Moreover, the use of auditory stimuli during the execution of the movement as an attentional strategy revealed compensate the movement difficulties in PD patients (Fernandez-

Del-Olmo et al., 2013; Horin et al., 2020; Ma et al., 2009; Rose et al., 2019; Sacrey et al., 2009; Sacrey et al., 2011; Vercruysse et al., 2012).

On the other hand, complex auditory stimuli, such as those containing semantic components, supposed to increase cognitive demand, showed impair the movement performance (Ma et al., 2009). However, auditory stimuli with lower cognitive attention load, such as those with instrumental and rhythmic components, exhibited the potential to entrain and synchronize the motor action of PD patients (Rose et al., 2019). The use of music without a rhythmic component as an attentional strategy showed no effect on the patients' motor action (Sacrey et al., 2009; Sacrey et al., 2011).

In addition, synchronization-continuation task (the movement must follow the sound rhythm; after a certain time, the auditory stimulus is turned OFF and the movement must continue to be performed at the same rhythm as the sound signal), that require more attentional and perceptual-motor demand, in the absence of the auditory signal showed impair of the performance of the motor action by the PD patients (Vercruysse et al., 2012). On the other hand, presentation of the auditory stimulus simultaneously with a visual stimulus showed decrease the cognitive load by generating an intersensory facilitation (Fernandez-Del-Olmo et al., 2013).

Neurobiological system

The studies showed that the rhythmic pattern provided by the auditory stimulus has the potential to deviate the cortex-ganglia dopaminergic circuit, which is dysfunctional in PD and important for the control of voluntary movement (Braunlich et al., 2019; Buard et al., 2019; Heida et al., 2014; Janzen et al., 2019; Novak et al., 2006). Thus, studies argued that the BG would be less involved in motor action guided by external stimuli and other regions would be activated, such as the cerebellum (Heida et al., 2014), the premotor cortex (Novak et al., 2006) and parietal regions – gyrus bilateral angular, supramarginal gyrus and left Rolandic operculum; regions known for their spatial auditory functions, attention, pitch memory and rhythmic learning (Buard et al., 2019).

Furthermore, connections among neural networks were found during the performance of motor activity in the presence of auditory stimulus. Auditory regions showed connect to visual regions and the executive control cortical network (lateral prefrontal cortex, inferior and posterior parietal cortex, and middle frontal cortex), and the latter network showed connect to the motor-cerebellar network (Braunlich et al., 2019).

Table 1

Summary of findings from studies of auditory stimuli in patients with Parkinson's disease

Study	Treatment	Auditory stimuli	Motor activity	Sync. accuracy	Cont. accuracy	Results
Freeman et al. (1993)	ON	Clicks 1, 2. 3, 4, 5Hz by 30s	Movements of the wrist to produce tapping of the index finger	Impaired to 1, 3, 4, 5Hz	Decreased	Less able to synchronize accurately, greater reliance on external cues for rhythm formation.
Gueye et al. (1998)	ON	Warning signal	Point a target with the index finger	No	No	Shorter Reaction Time, longer Movement Time.
Ma et al. (2004)	ON	A call bell	Reach-to-write	No	No	Shorter movement time, higher peak velocity, lower ration of peak-to-average velocity, and lower movement variability.
Ma et al. (2009)	ON	Marching music, 96–100 beats/minute for 30s, 62.4dB, and weather forecast	Reach task	No	No	Music did not affect movement. Weather forecast leads to slower, less forceful, more on-line controlled and less efficient movement.
Nowak et al. (2006)	ON & OFF – bilateral STN stimulation	Metronome 75msec beeps	Grasp-to-lift movement	No	No	With STN stimulation OFF the auditory cues enabled speed up the rate of grip force and the lifting acceleration.

Study	Treatment	Auditory stimuli	Motor activity	Sync. accuracy	Cont. accuracy	Results
Sabaté et al. (2008)	ON & OFF	Metronome Slow: 30, 40, 50 beats/minutes Fast: 40, 120, 200 beats/minutes	Rotary movement of the hand and tapping of the index finger	No	No	High-frequency beats accelerated movements, no dopamine effect (only for rotatory movement of the hand).
Sacrey et al. (2009)	ON	Verbal instruction and music without RAS	Reach-to-eat	No	No	There was no effect of auditory stimuli.
Sacrey et al. (2011)	ON & OFF	Verbal instruction and music without RAS	Reach-to-eat	No	No	There was no effect of auditory stimuli, and medication state.
Vercruysse et al. (2012)	OFF	Auditory pacing (AP) 66 %< comfortable frequency <100, 130%	Bimanual finger tapping	No	Increased	Better performance for PD without FOG than to PD with FOG.
Del-Olmo et al. (2013)	ON	Auditory stimulus (AS) and Startling auditory stimulus (SS) 750Hz tone/30ms, 80dB (AS) and 130dB (SS).	Ballistic wrist flexion	No	No	Faster reaction for the SS.

Study	Treatment	Auditory stimuli	Motor activity	Sync. accuracy	Cont. accuracy	Results
Heida et al. (2014)	ON ON & OFF- DBS	Metronome 1.6, 3.2, 4.8Hz 10 to 16s	Move hand or foot between two dots, separated by 30cm on the table or floor.	Increased .	No	Synchronization for all frequencies. Reduced action tremor for 1.6 e 4.8Hz.
Braunlich et al. (2019)	ON	RAS and verbal instruction Simultaneous alternating pure tones, 300Hz and 400Hz	Finger tapping, two speed (1Hz and 4Hz)	Decreased	No	Better performance for 4Hz movement.
Buard et al. (2019)	ON & MEG	Acoustic burst stimuli 2000Hz, 70dB for 30ms	Finger tapping	Increased after stimulation	No	There was no effect of the auditory cue on the performance.
Janzen et al. (2019)	ON	Metronome 1kHz, 85dB	Finger tapping and arm swing	Increased for finger tapping	No	Better performance for finger tapping.
Rose et al. (2019)	ON	Instrumental music with RAS and Metronome Slow: 69, 77, 81, 85 Medium: 112, 117, 120	Finger tapping	Increased for music (medium) and metronome (fast).	Increased for metronome (medium) and music (fast).	There was effect for medium and fast frequencies. Greater variability in all frequencies.

		Fast: 125, 136, 139, 144 beats/min.				
Study	**Treatment**	**Auditory stimuli**	**Motor activity**	**Sync. accuracy**	**Cont. accuracy**	**Results**
Wu et al. (2020)	ON	Pure tone 600Hz, 50ms, 70dB delivered each 800ms.	Finger tapping	Increased	No	Better performance.
Horin et al. (2020)	ON	A piano arrangement with RAS 100% of the preferred cadence	Finger tapping	No	No	Increase of the cadence and movement variability.

Note: PD = Parkinson's disease; ON = PD patient medicated; OFF = PD patient no medicated; STN = Subthalamic nucleus; RAS = Rhythmical auditory stimulation; FOG = Freezing of gait; DBS = Deep brain stimulation; MEG = Magnetoencephalography.

3.3 Discussion

Overall, the studies showed that RAS has an immediate effect on the upper limb movement performed by PD patients, resulting in improved performance. This finding was observed in patients in distinct stages of PD and in different treatment conditions (dopaminergic medication and/or DBS). The results also showed the effects of RAS on motor activity when presented only at moment before and onset of movement, or when it was presented during the entire execution of the motor task; its effect would be related to the potential of the auditory stimulus to deflect dysfunctional BG and activate other brain regions involved in the production of the action.

The characteristics of study participants were diverse. In some studies, relevant information was not found, which could contribute to expand the understanding of the results, such as the stage of the disease (Braunlich et al., 2019; Buard et al., 2019; Freeman et al., 1993; Heida et al., 2014; Nowak et al., 2006) and its duration (Braunlich et al., 2019; Buard et al., 2019; Sacrey et al., 2009; Sacrey et al., 2011). Furthermore, in most studies, the PD patients were in the ON period of medication at the moment of the task (Braunlich et al., 2019; Buard et al., 2019; Fernandez-Del-Olmo et al., 2013; Freeman et al., 1993; Gueye et al., 1998; Horin et al., 2020; Ma et al., 2004; Ma et al., 2009; Rose et al., 2019; Sacrey et al., 2009; Wu et al., 2020), which limits the possibilities of comparison and analysis of the effects of RAS in the studied population, considering the interaction of the auditory stimulus with the neurochemical condition.

The tasks used in the studies ranged from simple voluntary movements, such as tapping with the index finger of one or (Braunlich et al., 2019; Buard et al., 2019; Freeman et al., 1993; Horin et al., 2020; Janzen et al., 2019; Rose et al., 2019; Sabaté et al., 2008; Wu et al., 2020) both hands (Vercruysse et al., 2012), pointing with the index finger at a target (Gueye et al., 1998), swinging the arms (Janzen et al., 2019), rotating the hand (Sabaté et al., 2008) or moving it between two points (Heida et al., 2014), and flexing the wrist (Fernandez-Del-Olmo et al., 2013) to more complex sequential functional movements such as reaching-to-grasping task (Ma et al., 2004; Ma et al., 2009; Nowak et al., 2006; Sacrey et al., 2009; Sacrey et al., 2011).

Interestingly, PD patients showed benefit from rhythmic auditory cue during the execution of repetitive motor sequences, such as finger tapping (Horin et al., 2020; Rose et al., 2019). This type of movement seems be more subject to sensorimotor synchronization, that is, moving in the same beat as a rhythmic stimulus (Braunlich et al., 2019; Buard et al., 2019; Freeman et al., 1993; Heida et al., 2014; Janzen et al., 2019; Rose et al., 2019; Vercruysse et al., 2012; Wu et al., 2020). Although the finger tapping task depends on the same fundamental neural mechanisms involved in more complex motor behavior, the latter was less likely to benefit from the presence of the auditory stimulus. In the reach-to-grasp tasks performed in the presence of music with and without RAS (Ma et al., 2009; Sacrey et al., 2009; Sacrey et al., 2011), there was no effect of the stimulus on the movement, probably because these tasks are not as rhythmic as finger tapping. To reach and grasp an object it is necessary to plan and execute sequential movement, parallel control of the grip and lift force exerted by different muscle groups (Nowak et al., 2006), attention and sensory monitoring, as visually monitored limb advancement, grasping, limb withdrawal and releasing of the object are guided by somatosensory feedback, which requires constant shift in sensory control (Sacrey et al., 2011). These data suggest that the impact of the auditory stimulus may depend on the type of movement. However, the type of auditory stimulus is also an element that must be considered.

The auditory stimulus used in the studies were diverse, which, on the one hand, allows us to verify that diverse types of sound stimuli can modify the upper limb movements of PD patients, on the other hand, changes in movements may depend on the characteristics of the auditory cues, so that may be more effective than others. Music without RAS showed no affect PD patients movement on a reach-to-grasp task, regardless of disease stage and medication treatment (Sacrey et al., 2009; Sacrey et al., 2011). Similarly, music incorporated with RAS presented no significant effect on PD patients reach-to-grasp task performance (Ma et al., 2009); however, it showed improve movement in the tapping task (Horin et al., 2020; Rose et al., 2019). A key factor to note is that, although music may have a strong beat, this may not be enough to affect the PD patient's movement, as studies revealed that the PD patient's movement rate can be slower or faster than rhythm of the music (Horin et al., 2020; Ma et al., 2009; Rose et al., 2019).

Also, the performance of the PD patient's movement can be influence by collative properties present in music, such as familiarity, pleasantness, complexity, and affective states (Rose et al., 2019). In addition, there is evidence that such properties can affect attentional focus. Sacrey et al. (2009) and Sacrey et al. (2011) observed a potential in music to normalize the shifting of sensory attention during reaching movement in PD patients. They suggested that music may have a general arousing effect by impacting dopamine release, cerebral blood flow and activating a non-specific auditory arousal system, which in turn facilitates motor activity.

Among the studies that used the metronome as a resource to offer RAS, all of them found the effect of sound stimulus on the motor activity of the upper limb of PD patients (Heida et al., 2014; Janzen et al., 2019; Nowak et al., 2006; Rose et al., 2019; Sabaté et al., 2008). Considering that the frequencies used in the studies varied, it can be assumed that motor patterns change according to the frequency of the sound beat. Sabaté et al. (2008) found that the speed of the rotating hand movement, performed by PD patients, decreased with the increase in the frequency rate. Likewise, Rose et al. (2019) observed that all participants (including the non-PD) had significantly more movement asynchrony in the slow frequency condition when compared to the medium and fast tempi conditions. Also, with the use of DBS, frequency revealed affect motor action. Heida et al. (2014) found differences in the synchronization of hand movements, performed by PD patients with DBS, for three sound frequencies (1.6Hz, 3.2Hz, and 4.8Hz). The movement becomes synchronized with the auditory cue at the frequency of 1.6Hz, when in the absence of tremor. In contrast, when tremor was present, the 4.8Hz frequency produced a higher level of movement synchronization with the sound beat. And the 3.2Hz auditory signal showed a tendency to synchronization, also in the presence of tremor.

Furthermore, the effect of music and metronome on movement may be related to the type of motor activity (Horin et al., 2020; Ma et al., 2009; Rose et al., 2019; Sacrey et al., 2009; Sacrey et al., 2011;). Janzen et al. (2019) observed that PD patients had more difficulty maintaining the tempo set by the metronome in the arm swing task than in the finger tapping task. In the study by Rose et al. (2019), it was found that stepping on the spot was better than finger tapping and toe tapping for entrainment, synchronization, and pace stability; with the music favoring synchronization more than the metronome. According to the authors (Janzen et al., 2019; Rose et al., 2019), the effect of RAS may be subject to biomechanical properties, such as limb length and mass distribution, efficient oxygen consumption and muscle activity, so that, movements may be less susceptible to rhythmic priming than others.

Besides the use of music and metronomes as auditory stimuli, the studies used auditory cues such as clicks (Freeman et al., 1993), auditory warning signs (Gueye et al., 1999), bell ring (Ma et al., 2004), startling auditory stimuli (Fernandez-Del-Olmo et al., 2013). In general, these sound stimuli showed a significant effect on upper limb movement in PD patients (Braunlich et al., 2019; Buard et al., 2019; Fernandez-Del-Olmo et al., 2013; Freeman, et al., 1993; Gueye et al., 1999; Ma et al., 2004; Vercruysse et al., 2012; Wu et al., 2020). However, some of them showed no improve motor action (Ma et al., 2009), corroborating the assumption that motor response may be dependent on the properties present in the sound stimulus. It was found that auditory stimuli, which require semantic processing, can cause a decline in motor performance, as when listening to the semantic content, the focus of attention would be redirected from the motor task. (Ma et al., 2009).

Auditory stimuli demonstrated not only to affect motor performance of PD patients, but also to influence cognitive functions, more specifically, attentional capacity, and sensorial perception (Fernandez-Del-Olmo et al., 2013; Gueye et al., 1998; Horin et al., 2020; Ma et al., 2004; Ma et al, 2009; Nowak et al., 2006; Rose et al., 2019; Sacrey et al., 2009; Sacrey et al., 2011; Vercruysse et al., 2012). Studies pointed out that when a movement must be performed after a sound cue, the auditory signal serves as an aid to draw attention to the task (Gueye et al., 1998; Ma et al., 2004; Nowak et al., 2006). Similarly, when a dual task is proposed, that is, when listening to an auditory stimulus and performing a motor activity must occur simultaneously, the attentional component can become inherent to the task (Horin et al., 2020; Ma et al, 2009; Rose et al., 2019; Sacrey et al., 2009; Sacrey et al., 2011; Vercruysse et al., 2012). Besides, when the sound stimulus is present simultaneously with another modality of sensory stimulus, such as visual signals, intersensory perception can improve of attention and modulate the performance of the motor task (Fernandez-Del-Olmo et al., 2013).

Considering that the motor preparation strategy would involve attentional processes and depend on external and internal stimuli, Gueye et al. (1998) argue that an auditory cue, such as a warning signal, given in an advanced for the performance of a movement can serve as a preparatory signal to focus attention of PD patients. It is important to highlight that the auditory stimulus, in the Gueye's study, not only indicated the moment of the movement's beginning, but also indicated where the movement should be direct. Ma found a similar result et al. (2004), in their study, a single warning signal (a call bell) triggered prior to the task and used to draw attention, significantly affected, and had a large effect on the PD patient's sequential movement (reaching a pen to write). The authors suggest that patients had problems with self-initiated movement and providing a single external timing cue facilitated their performance. Also, Nowak et al. (2006) observed that the presentation of a single auditory cue for movement initiation improved the kinematics of the grasping and transport movements and speed up sequential movements of the hand and arm in PD patients.

Moreover, evidence showed that providing external auditory cues not only for the initiation of movement, but also during its execution, leads to an improvement in motor activity in PD patients (Ma et al., 2009). Ma et al. (2009) investigated the use of external sensory stimulus as attentional strategy to compensate for the difficulty of movement in PD patients. They asked patients to perform a reach-to-transport task in the presence of marching music or weather forecast, in three conditions: no auditory stimulus, listening to the auditory stimulus, and ignoring the auditory stimulus. The findings showed that the marching music had no effect on the kinematics of the movement. In contrast, the weather forecast produced a decline in performance when participants were instructed to listen to the weather forecast than when they were instructed to ignore it or when no weather forecast was provided. However, while the attentional load of rhythmic instrumental music associated with performing the task did not seem to adversely affect the movement, the same was not observe for the weather forecast. According to the authors, listening to the forecast while executing the motor task requires complex cognitive functions, such as semantic processing and working memory, which exceed the available attentional resource capacity of patients. In addition, the authors emphasize that paying attention to the sound or ignoring it influences the task performance. PD patients performed the task better when they ignored the auditory stimulus than when they listened to it.

Rose et al. (2019), when investigated how different sound cues (music and metronome) affected rhythmic motor behavior of PD patients, observed that music helps the PD patients maintain entrainment when compared to the metronome, especially in the absence of external sound cue (synchronization-continuation task), after it has been used to initiate the movement and indicate the rhythm. The authors argue that the music used did not generate a demand cognitive. Patients reported liking the music more than the metronome, and they stated that continued to sing the music in their minds as the task continued in the absence of song. Based on this, the authors hypothesize that the rhythmic repetition of music (instrumental or lyric) induces a priming effect. But they caution about the potential distraction music can have, as some patients reported feeling that the music 'pushed then out of the way.' Horin et al. (2020) found that PD patients, in O**N** medication, performed gait, finger tapping and foot tapping with lower movement variability in response to self-generated cues than in the presence of music with a prominent beat. The self-generated cues consisted of the participants listening to the song once and then mentally singing the song while performing the movement, following the beat of their mental sing. This result, associated with the result found by Rose et al. (2019), seems to point out that keeping music in mind (that is, singing mentally) can facilitate motor activity.

On the other hand, the association of cognitive load and motor complexity for PD patients seemed to impair the motor action. Vercruysse et al. (2012) observed that patients with

FOG benefited from auditory pacing in a bimanual finger tapping task, in which movement, amplitude, and frequency were manipulated to add complexity to motor coordination; however, cue removal generated finger movements with small and unstable amplitude, variable and hastened frequency, and decreased coordination stability. The authors suggest that increase attentional and perceptual-motor demands led to a defective organization of the ongoing movement of PD patients with FOG, in contrast to movement produced by PD patients without FOG or participants without the disease.

Furthermore, it was observed that sensory-motor integration can influence the attention demand and produce a positive effect on movement. Sacrey et al. (2009) and Sacrey et al. (2011) found that the preferred musical pieces without RAS did not improve the biomechanical measures of reach nor the movement elements scoring in the reach-to-eat task performed by PD patients. However, music did influence shifting attention from vision to somatosensory orientation to grasp food and bring it to the mouth. Sensory attention shifting improved when the PD patients was medicated and listening to music. In addition, offering auditory stimulation simultaneously with visual stimulus can induce an improvement in PD patients' movement because of intersensory facilitation (Fernandez-Del-Olmo et al., 2013).

Considering the neurobiological process, entrainment and synchronization demonstrated to be the basis of the effect of music on PD patients' movement. Studies reported that the rhythmically structured sound pattern creates an anticipatory of beat-marked time sequence template that can facilitate movement by enabling the timing of muscle activation to be entrainment and synchronized with the temporal structure of beats (Heida et al., 2014; Nombela et al., 2013; Novak et al., 2006). In this process, alternative pathways seem to be activated during motor activity in response to the auditory cue, which would provide compensatory mechanisms for impaired motor loops in PD (Novak et al., 2006). Novak et al. (2006) found that external auditory timing cues improved the peak rates of grip force and the accelerations of the lifting movement of the PD patients OFF STN-DBS in a grasp-to-lift task. According to the authors, the results showed that BG are less involved in the control of externally guided movements, with the motor action being planning and executed by the premotor cortex, which is under significantly less input from the BG. Likewise, Heida et al. (2014) propose that repetitive movements guided by external cues performed by PD patients lead to the activation of the cerebellum. Buard et al. (2019) analyzed the neural activity of PD patients performing a motor task and found that the patients relied on a greater extent to the bilateral angular and supramarginal gyri, and the left Rolandic operculum, parietal areas which compound the network involved in auditory spatial and attention functions, in rhythm learning and pitch memory. Also, it was observed that inter-network connectivity was stronger for PD patients, during rhythmic motor performance (finger tapping task) in presence of RAS, than for healthy controls, especially between the auditory-visual networks, the auditory-executive control networks, and the motor/cerebellar-executive control networks (Braunlich et al., 2019). It is well known that executive control depends on brain regions that include lateral prefrontal, inferior parietal, posterior parietal, and medial frontal cortexes (Braunlich et al., 2019). It is important to mention that there was no effect of RAS, of the tapping speed, or of the participants group on functional connectivity within the basal ganglia/thalamus region or between this area and other brain networks, which seems to confirm that auditory stimuli have the potential to deviate the BG.

Janzen presented interesting finding et al. (2019). They observed that PD patients who undertook 4-minute auditory-motor training consisting of finger tapping to a metronome set to 20% faster than the pre-training walking cadence showed significant increase in gait velocity and cadence in the post-training assessment. To authors, the results indicate that auditory-motor entrainment in one effector system (i.e., finger tapping), may prime a second effector system (i.e., gait). This rhythmic priming across effector systems would be associated with a widespread modulation of cortical auditory-motor interconnectivity with distributed effects. Thus, the entrainment observed in the finger tapping task could have generated a residual resonance or secondary entrainment that affected adjacent interconnected neurons leading to a priming effect on gait.

Considering the effect of dopaminergic medication, Wu et al. (2020) observed that synchronization stability did not significantly differ between the PD patients ON medication and control participants when the task was performed in the presence of beats consisting of auditory tones. The authors argue that the effect of dopaminergic medication would has contributed to the lack of differences. However, this study did not include patients without dopaminergic medication, thus it was not possible directly test the hypothesis suggested by them. Other studies did not find group difference for the auditory beat synchronization in PD patients in ON medication (Buard et al., 2019; Rose et al., 2019). However, some studies showed that medicated PD patients are less exact than non-PD participants in replicating the cue frequency and in producing an even pace (Freeman et al., 1993; Vercruysse et al., 2012). Studies, which compared to PD patients in OFF and ON medication, no mention was found to synchronization effect or differences in motor activity performed in the presence of RAS (Sabaté et al., 2008), and the music had no effect on the reach-to-grasp task performed by PD patients independently of the medication condition (Sacrey et al., 2011).

In summary, studies point out that, although some specific characteristics of auditory stimuli must be taken into account for their effect on movement in PD patients, such as salient beat and complexity, their use is not limited to a single type of stimulus, but to a variety of options. Some of them may have a better effect on certain movements and their kinematic aspects and others may have influence on other factors related to the movement performance. Therefore, considering the combination of sound stimulus and motor task to obtain the desired result seems to be essential for the effectiveness of using the external auditory cue to improve the motor performance of PD patients. In addition to this, one must also consider the cognitive components, such as the attentional demand, involved both in the performance of the movement and in the processing of the auditory stimulus. Moreover, the interaction between different neural networks has been showing to be involved in the effect of the auditory stimulus on movement. Particularly in PD patients the interactions between the circuits showed that dysfunctions in the BG can be overcome, and other systems come into play.

However, there is no unanimity among the results of studies about which sound stimuli affect movement in PD patients. This can be due to the diversity of methods used in research. It is true that studies, in addition to those discussed here, have been developed on the subject, however, the purpose of this review was not to exhaust the topic.

More studies, including homogeneous protocols, are needed to determine which type and characteristic of auditory stimuli are best suited to promote benefits on movement; besides, which motor activities would be more susceptible to obtain improvement according to the distinct stages of PD.

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4 The complexity of an artwork affects the subjective perception of time and bimanual motor activity performed in the presence and absence of music by patients with Parkinson's disease

The subjective representation of the passage of time is critical to human existence. In fact, all behaviors occur over time and, as a result, time is an implicit dimension of everyday experience, such as movement, decision making, and activity planning. For example, remembering a past event, its location, and its contextual associations to judge how recent the event is, or estimating the amount of time elapsed between a past and present event, or the ability to formulate plans, retaining them in memory and executing them at a certain point in time or for a certain duration (Grondin, 2010).

However, unlike light or sound, time has no specific organ or sensory system. Previous and ongoing research has been developing with the aim of better understanding psychological time and temporal information processing. In general, these studies ask participants to judge a certain time explicitly, and for this, two paradigms are use. In the prospective paradigm, participants are informed prior to the task that they must make a judgment of time, so the duration experienced is estimated. In contrast, in the retrospective paradigm, participants do not receive any prior notice, they are asked to make a time estimate after performing the task, thus judging a remembered duration (Jones & Jahanshahi, 2014).

Based on these paradigms, different methods have been proposing to assess the perception of time. Traditionally, four main methods are used: (a) verbal estimation, in which the participant provides a verbal estimate of the event, using temporal units such as seconds or minutes; (b) temporal reproduction, in which an event is experienced and the participant reproduces the duration of the event by some operation, such as pressing a button to start and pressing it again to indicate the end of the estimate; (c) time production, in which a specific time interval is determined and the participant produces this interval; (d) comparison method, in which the participant must judge the duration of the interval presented by comparing them with a second interval, indicating whether the interval presented was shorter or longer than the first (Grondin, 2010; Jones & Jahanshahi, 2014).

Theoretical models of time judgment have been proposing to explain how this mechanism occurs. In general, they rely on a central mechanism (pacemaker-counter) responsible for estimating time (Treisman, 1963). A traditional model is the *Internal Timer Model or Scalar Expectancy Theory* – SET (Church, 1984; Gibbon et al., 1977; Matell & Meck, 2000; Treisman, 1963). This model proposes that during an experience to-be-timed, pulses are produce at a specific rate by a pacemaker and sent to an accumulator by a switch (perceptual or clock system). The number of pulses is compared with the duration reference stored in long-term memory (memory system) and determines the perceived length of the interval (decision system). This estimation would have a scalar property, that is, the coefficient of variation would remain stable along the intervals by a positive correlation between the standard deviation of an estimated interval and the mean interval length. Since the temporal processing would involve the Basal Ganglia (BG), dopaminergic circuits and prefrontal areas.

Other models were proposed. The *Storage Size Model* (Ornstein, 1975), which states that a large amount and high complexity of information require a large space in memory, thus generating long time estimation. The *Attentional Model* (Hicks et al., 1976), whose attentional component would be involved in the temporal information processing. Thus, the more attention is allocated to the non-temporal task, the less attention is direct to time, and fewer pulses are produced, leading to a perception of the experienced duration as being shorter than the objective time. The opposite is also true. The *Contextual Change Model* (Block & Reed, 1978), which states that the remembered duration involves a cognitive reconstruction of the environmental information surrounding the stimulus: more remembered contextual changes cause longer time estimates. The *Expectation Model* (Jones & Boltz, 1989), which predicts that a sequence of events ending at the "right time" would confirm expectations and produce quasi-precise estimation. A sequence of events ending later than expected would seem longer and lead to overestimation. A sequence of events that end earlier than expected would elicit underestimation. Moreover, other theoretical propositions to explain the ability to perceive the time passing. For instance, Firmino and Bueno (2008) do not refer to any type of pacemaker or oscillations to explain the subjective time perception, instead, in the model called *Expected Development Fraction* (EDF), the authors assume that expectations about an event, such as sudden and gradual modulations in a musical stimulus, will develop expectations, extending the duration perception and leading to alterations in subjective time judgment. Matthews and Meck (2016) provided the *processing principle*, which considers that the subjective duration of a stimulus is positively related to the strength of its perceptual representation. The vividness of the experienced event and the clarity of perception (i.e., the stimulus properties that shape non-temporal perception) would make it easier to extract information from that event, hence would facilitate perceptual decisions and would expand the apparent duration of the event. "That is, the processes and variables that make a percept subjectively more vivid and objectively easier to identify, categorize, and evaluate also make it seem to last longer" (Matthews & Meck, 2016, p. 869). The process is a confluence of received sensory information, attention allocation and memory process.

Furthermore, a field of research that has investigated the subjective time perception is the *New Experimental Aesthetics*, which consists in the study of the artworks through scientific empirical methods to evaluate their effects on behavior (Berlyne, 1958, 1963, 1974). Studies in this area have revelated that the appreciation of artworks, such as music (Firmino & Bueno, 2016; Ramos & Bueno, 2012;), visual art with movement suggestion (Nather & Bueno, 2011, 2012), and sculptures (Motta et al., 2019) have the potential to change the perception of time.

In this field, attributes of artworks can be manipulated. These attributes named by Berlyne (1958, 1963) as collative properties, such as familiar-unfamiliar, complex-simple, regular-irregular, interesting- uninteresting. Specifically, the complexity of a stimulus can be established by the amount of material or variety of pieces, irregularity of shape or arrangement. In general, Semantic Differential Scales are used to evaluate the collative properties. Therefore, the use of sculptures manipulated in their properties can contribute to investigations about the subjective time perception. Mainly, considering the possibility of manually exploring these sculptures. Motta et al. (2019) conducted a study in which analyzed the effects of manipulating two artworks with distinct levels of complexity on the time perception of Parkinson's disease (PD) patients. The task was to manipulate one artwork at a time for the desired amount of time. After the task was complete, PD patients and non-PD participants were asked to make a verbal estimation of the duration of manipulation each artwork. The quality of motor exploration was analyzed. The findings showed that the duration of manipulation was overestimate by PD patients and non-PD. Despite the absence of statistical significance, PD patients had a lower estimation of manipulation time compared to non-PD participants. In addition, PD patients exhibited lower quality of exploration of artworks than non-PD. The results were attribute to impairment of motor activity in PD patients associated with perceptual and cognitive deficits.

It is known that PD is a neurodegenerative disorder that results in motor alterations, the ones being tremor at rest, rigidity, bradykinesia, and postural instability, and, in autonomic, cognitive, psychiatric, and sensory alterations (Armstrong & Okun, 2020). Parkinson's disease is characterized by basal ganglia (BG) dysfunction due to death of dopaminergic neurons in the substantia nigra par compact and a depletion of dopaminergic neurons that project to the caudate-putamen (striatum nucleus Tarakad & Jankovic, 2017). The BG and its dopamine-dependent thalamocortical pathway, in addition to being involved in motor control, have been consider essential in the temporal information processing (Harrington & Jahanshahi, 2016; Matell et al., 2003; Nenadic et al., 2003). Studies have investigated the time perception in PD patients. Regarding verbal time estimation, one study found underestimation in PD patients (Pastor et al., 1992). Two other studies found no differences in the verbal temporal judgment of PD patients compared to non-PD participants, however, one of them reported that participants overestimated the time, with the PD patients showing less overestimation (Motta et al., 2019) and another indicated that participants underestimated the duration (Riesen & Schnider, 2001). Furthermore, Wearden (2008; 2009) found similar performance between the participants with and without PD, all of whom were accurate in estimating time. Regarding the temporal reproduction, PD patients on ON medication (period of about 30 to 60 minutes after ingestion of the dopaminergic drug) and OFF medication (period of 12-14 hours without ingestion of dopaminergic medication) showed a beneficial effect of the medication on the patients' time perception (Pastor et al., 1992; Malapani et al., 1998; Koch et al., 2005, Honma et al., 2016). In addition, PD patients with deep brain stimulation in subthalamic nucleus (DBS-STN) had a positive effect of the treatment condition on temporal perception (Koch, Brusa et al., 2004; Torta et al., 2010). There is evidence that dopamine can allow compensatory activation in the cortical region, which would reflect a more accurate time perception (Dušek et al., 2012). On the other hand, Wearden et al. (2009) found that PD patients shown not to be affect by the medication status (OFF and ON medication) in the time perception task. However, dopaminergic treatment has been showing to improved cognitive performance, such as memory (Malapani et al., 1998; Malapani et al., 2002; Perbal et al., 2005), attention (Motta et al., 2019; Riesen & Schnider, 2001; Torta et al., 2010) and executive function (Artieda et al., 1992; Jahanshahi et al., 2010; Ogden et al., 2011; Merchant et al., 2008). All cognitive processes involved in processing temporal information. Perbal et al. (2005) found that PD patients who reproduced the shortest durations were those with the lowest score for delayed recall on a neuropsychological test.

It is important to mention that aspects related to the motor activity of the PD patients can influence the time perception. Studies have appointed that counting time, internally or aloud, has been identifying as a factor that would affect temporal judgment in PD patients (Jones et al., 2008; Wearden et al., 2008; Pastor et al., 1992). The finger tapping task performed simultaneously with the time perception altered the temporal perception of PD patients (Honma et al., 2016) or was like the performance of non-PD participants (Riesen & Schnider, 2001). Moreover, in a motor task in which motor response time was assess, Jones et al. (2008) found that patients were as effective as participants without PD. On the other hand, in a complex motor activity (unscrewing a screw nut), PD patients had impairment in reproducing the duration of their motor actions, while they accurately reproduced the duration of a time interval (Torta et al., 2010).

Regarding motor function in PD patients, different cueing strategies have been using to improve the motor performance of this population (Heida et al., 2014; Ma et al., 2004; Nowak et al., 2006; Rose et al., 2019; Sabaté et al., 2008;). It has been proposing that rhythmic cue, such as rhythmic auditory stimulation (RAS), may deviate the motor deficits of the PD patients, thus compensating for the deficient internal cue function of the BG (Horin et al., 2020; Janzen et al., 2019; Rose et al., 2019). The effect of RAS occurs as result of the human ability to extract rhythm from the external world (Ashoori et al., 2015; Erra et al., 2019), which is an entrainment mechanism. It can be defined as the coupling process between systems. RAS generates a firing rate in the auditory system that entrains the firing rate of the motor system, producing the synchronization of motor activity with the beats of the sound cue. The result is movement time aligned simultaneously to a specific point with the pacing source (Buard et al., 2019; Janzen et al., 2019; Nombela et al., 2013; Rose et al., 2019). This mechanism has the potential to bypass dysfunctional BG in PD patients (Thaut et al., 2015).

However, in general, most research investigating the effects of external cues on motor tasks in PD patients seems to focus on locomotion (i.e., gait), with fewer studies on rhythmic timing and upper limb tasks, despite the importance of manual function for the quality of life of PD patients with the improvement in the performance of tasks such as dressing, eating, etc. (Ringenbach et al., 2011). Therefore, there is a need for more research to investigate the influence of distinct types of cues on bimanual task of PD patients. Associated with this, although the scientific literature show studies that address the relationship with auditory cue and motor action (Nombela et al., 2013), time perception and auditory stimuli (Jones et al., 2008; Wearden et al., 2008), and temporal perception and motor activity (Motta et al., 2019), to our knowledge, no studies were found that investigated the relationship between bimanual task, music incorporated with RAS and subjective time perception in PD patients, particularly when they are in the OFF and ON medication state.

Therefore, the main purpose of this study was to examine whether music with RAS can influence upper limb movement in PD patients in OFF and ON state medication, and whether this experience, which relates auditory stimulus and motor function, would influence the temporal reproduction and the verbal time estimation of these patients. This is because everyday life is full of various sounds, so it is important to investigate whether these sounds function as external auditory cues that facilitate motor performance and judgment of duration. Furthermore, considering that the cognitive function participates in the temporal information processing, we aimed to correlate the temporal estimate and scores of neuropsychological tests. Below our questions (MCA = more complex artwork); LCA = less complex artwork; ON = PwPD medicate; OFF = PwPD no medicate; TR = temporal reproduction; VE = verbal estimation):

Question 1

Music affects the manipulation of $\dfrac{\text{MCA}}{\text{LCA}}$ of PwPD in $\dfrac{\text{ON}}{\text{OFF}}$?

Question 2

Music affects the perception of time manipulation $\dfrac{\text{TR}\ \dfrac{\text{MCA}}{\text{LCA}}}{\text{VE}\ \dfrac{\text{MCA}}{\text{LCA}}}$ of PwPD in $\dfrac{\text{ON}}{\text{OFF}}$?

Question 3

There is a correlation between the $\begin{matrix}\text{TR/}\\ \text{VE}\end{matrix}\ \dfrac{\text{MCA}}{\text{LCA}}$ score of the neuropsychological tests ?

For answer these questions, music with a salient beat and verbal instruction was present when PD patients manipulated two artworks with different level of complexity. The choice of manual motor task aimed to reflect more closely the performance of PD patients in daily life and to verify whether different collative properties of the manipulated object reflets on the time perception and movement of these patients. Movement frequency analyzes were used, which allowed detecting the quality of movement performed by the participants. The hypothesized was that the effect of music on the time perception would be greater in PD patients on OFF than on ON medication, and greater PD patients when compared to non-PD participants. In addition, music would induce the improvement of the motor task for PD patients and the distinct levels of complexity of the artworks would influence the temporal duration perception and the movement of patients.

4.1 Methods

Participants

Twenty-three PD patients (19 male; 4 female) and 22 non-PD participants (9 male; 13 female) participated in this study. The average age of the PD patients was 55.30 (mean)±6.9 (SD) years and did not differ from the age of the non-PD, which was 56.41±9.5 ($t(38.218) = -0.445$, $p = 0.659$). Also, the average years of study did not differ between groups, which was 9.6±4.8 to PD patients and 10±4.1 to no-PD ($t(43) = -0.358$, $p = 0.722$). The degree of motor impairment of the patients was assessed by the motor subscale of Movement Disorders Society-Unified Parkinson's disease Rating Scale" – (MDS-UPDRS-III. Goetz, 2010), in the OFF state the score was 38.49±3, and in the ON medication the score was 18.64 ±2.3 (paired t-test, $p < 0.001$). PD patients were evaluated while they were OFF and ON antiparkinsonian medication.

The PD patients were recruited from Ribeirão Preto School of Medicine Hospital, São Paulo, Brazil. An expert neurologist made the diagnosis of idiopathic PD according to the London Bank Criteria (Daniel & Lees, 1993). Exclusion criteria included (a) a Hoehn and Yahr (1967) score ≤ 2; (b) dementia based on clinical examination and by the Mattis Dementia Rating

Scale (Mattis, 1988), for which no significant difference between the two groups was found (lambda de Wilks = 0.87, p = 0.39); (c) significant history or current psychiatric disorders, historic of neurological disease (excluding PD) or peripheral neuropathy; (d) symptoms of depression moderate to severe assessed by the Beck's Depression Inventory - BDI-II ($F(1;40)$ = 3.77, p = 0.06. Beck et al., 1961; Gomes-Oliveira et al., 2012); (e) history of head trauma, stroke or epilepsy, and drug abuse or a history of substance abuse (including alcohol drink). The exclusion criteria for non-PD participants were the same as for PD patients, except for the ingestion of medications with effects on the central nervous system and, obviously, there was no Hoehn and Yahr score. All participants did not report any prior formal and systematic training in artistic activity, nor hearing deficits.

The Research Ethics Committee of the University of São Paulo approved the study (CAAE nº 68684917.6.0000.5407), and each participant signed an informed written consent upon inclusion in the study.

Neuropsychological tests were performed when PD patients were on ON medication. A properly qualified psychologist administered the tests. The following tests were applied:

Interlocking Finger Test. IFT is a screening test that consists of imitating four interlocking finger gestures without symbolic meaning, one at a time. It assesses parietal lobe dysfunction such as limb praxis, visual praxis, and visuospatial capacity, and visual-constructive capacity (Moo et al., 2003).

Digit Span Test. DST assesses working memory capacity considering the maintenance and manipulation of information. A list of numbers is read, and the participant had to repeat it in the order presented (maintenance component) and then in the reverse order (manipulation component; Grogan et al., 2018).

Mattis dementia rating scale. MDRS is a screening tool for detecting dementia. It sensitively assesses global cognitive status to measure the degree of frontal-subcortical deficits. It consists of 36 tasks divided into five subscales: Attention, Initiation / Perseveration, Construction, Conceptualization and Memory. Higher raw scores indicate better cognitive status (Llebaria et al., 2008; Porto et al., 2003).

Clox - Clock Drawing Test. The *C*LOX is a tool used to screen impaired executive control functions. It involves clock drawing (CLOX 1), in which the participant draws a clock, and copies the draw of a clock made by the examiner (CLOX 2). Lower scores reflect greater impairment (Atalaia-Silva & Lourenço, 2008; Royall et al., 1998; Shuman, 2000).

Verbal Fluency Test. The VFT is a test used to evaluate executive functions, attention, and language (Brucki & Rocha, 2004). There are two types of tests: (a) semantic VFT, in which the participant says as many words as belonging to a category, e.g., animals, and (b) the phonemic VFT, in which the participant says as many words as beginning with the letters F, A and S (FAS). The total final score includes only correct answers.

Bo*ston Naming Test*. BNT investigates language skills, including naming or retrieving words. It consists of 15 black and white line drawings of different images sorted according to three difficulty levels. The participant must name the figures within ten seconds. One point is credit for each correct answer (Kaplan et al., 1978; Miotto et al., 2010).

Frontal Assessment Battery. FAB is a brief screening tool for dysexecutive syndrome. It consists of six subtests: (a) similarities, (b) verbal lexical fluency (letter S), (c) motor series, (d) conflicting instructions (e) go/no go (f) prehension behavior (Beato et al., 2007).

Equipment and Material

Artworks. Two reproductions of artworks from the series *"Bichos"* by Lygia Clark (Butler & Pérez-Oramas, 2014) were used as experimental stimuli. The artworks were composed of flat pieces of 2-mm-thick frosted aluminum. Each piece had the geometric shape of a scalene triangle, with dimensions 26cm x 17cm x 14.5cm. The flat pieces were functionally related to each other, which allowed them to be moved in many configurations.

The artworks were manipulated in complexity level based in the number of pieces. The less complex artwork (LCA) had six flat pieces, and the more complex artwork (MCA) had 10 flat pieces (Figure 1 and 2). According to the collative properties of stimuli (see Berlyne, 1963, for more), the number of pieces in the stimuli can configure complexity to them. The attribution of complexity level of the stimuli was confirmed by participant judges in a previous study (Bueno et al., 2020).

Figure 1

Less Complex Artwork with six pieces

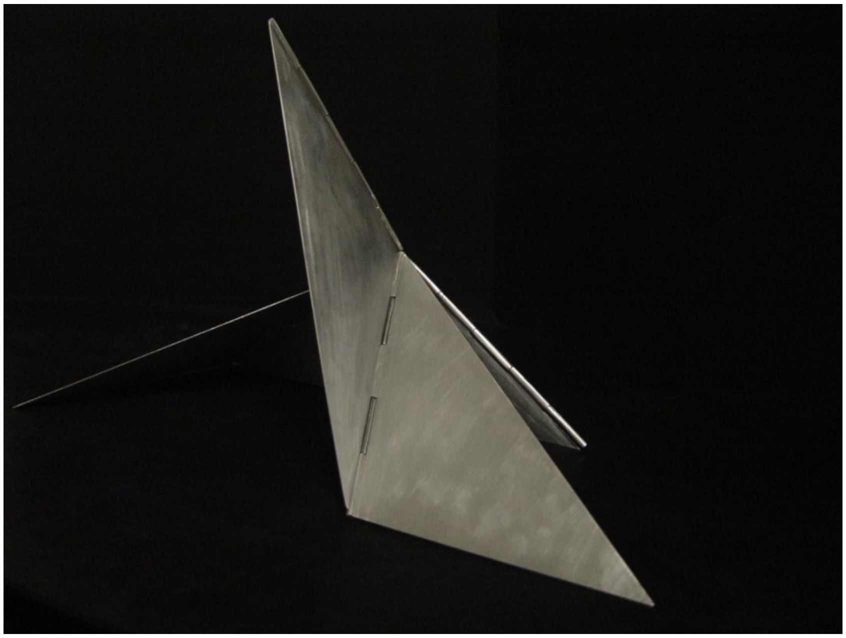
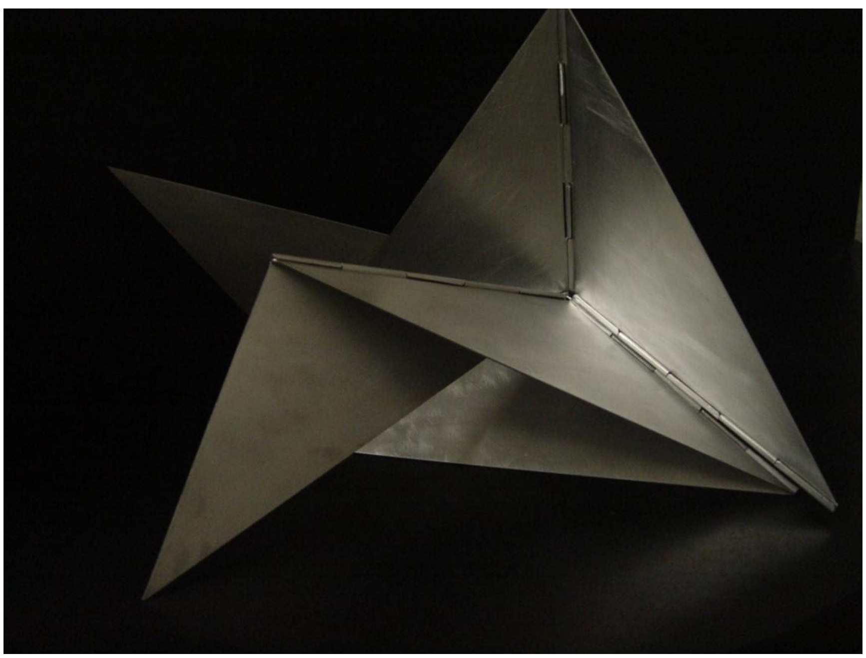


Figure 2

More Complex Artwork with ten pieces



The training stimulus was composed of one flat piece of 24mm-thick frosted aluminum, with the geometric shape of a scalene triangle, with dimensions 26cm x 17cm x 14.5cm, bent at a 90º angle height.

Auditory stimuli. Two conditions were applied: music condition and non-music condition. For the music condition, two instrumental music were used: *Sanfona Sentida* (Felt Accordion composed by Dominguinhos and Anastácia) and *O Casamento da Raposa* (The Wedding of the Fox composed by Gerson Filho), both performed by Nicolas Krassik. The songs were 45s long, and at equal intervals of time a verbal instruction with the command “Move the object” was declared by a female voice and superimposed on the music. For the non-music condition, the 44s was marked by two beeps spaced 45s apart, the same duration as the condition with music. Also, the same verbal instruction was declared during this condition.

Figure 3

The rotating bulkhead containing three compartments

Equipment. During the task, participants were seated in front of a rotating bulkhead containing three compartments (Figure 3). In each compartment, different artwork stimuli were placed (training stimulus, LCA and MCA). A Panasonic HDC-HS80 camcorder was attached to a rod 55cm above the manipulation site. The duration of the music presentation was controlled by the *Program Wave Surf* installed in a notebook (Positivo V146). To record the manipulation time reproduction, there was a button connected to the computer and positioned on the right side of the participant. The music was present through headphones (JBC model 55i).

Tasks of Time Perception and Manipulation of artworks

Participants were assigned randomly to one of two conditions: music condition or non-music condition. For all participants, the training stimulus was presented first, and the instruction was the same given for the task phase. Participants were expose to one artwork at a time, the order of presentation of each artwork was distribute randomly. Patients were evaluated first OFF medication and then ON medication. Considering experimental control there were two test sessions for the non-PD group, labeled "OFF" and "ON," as they were arbitrarily associated (yoked) with patients OFF/ON sessions.

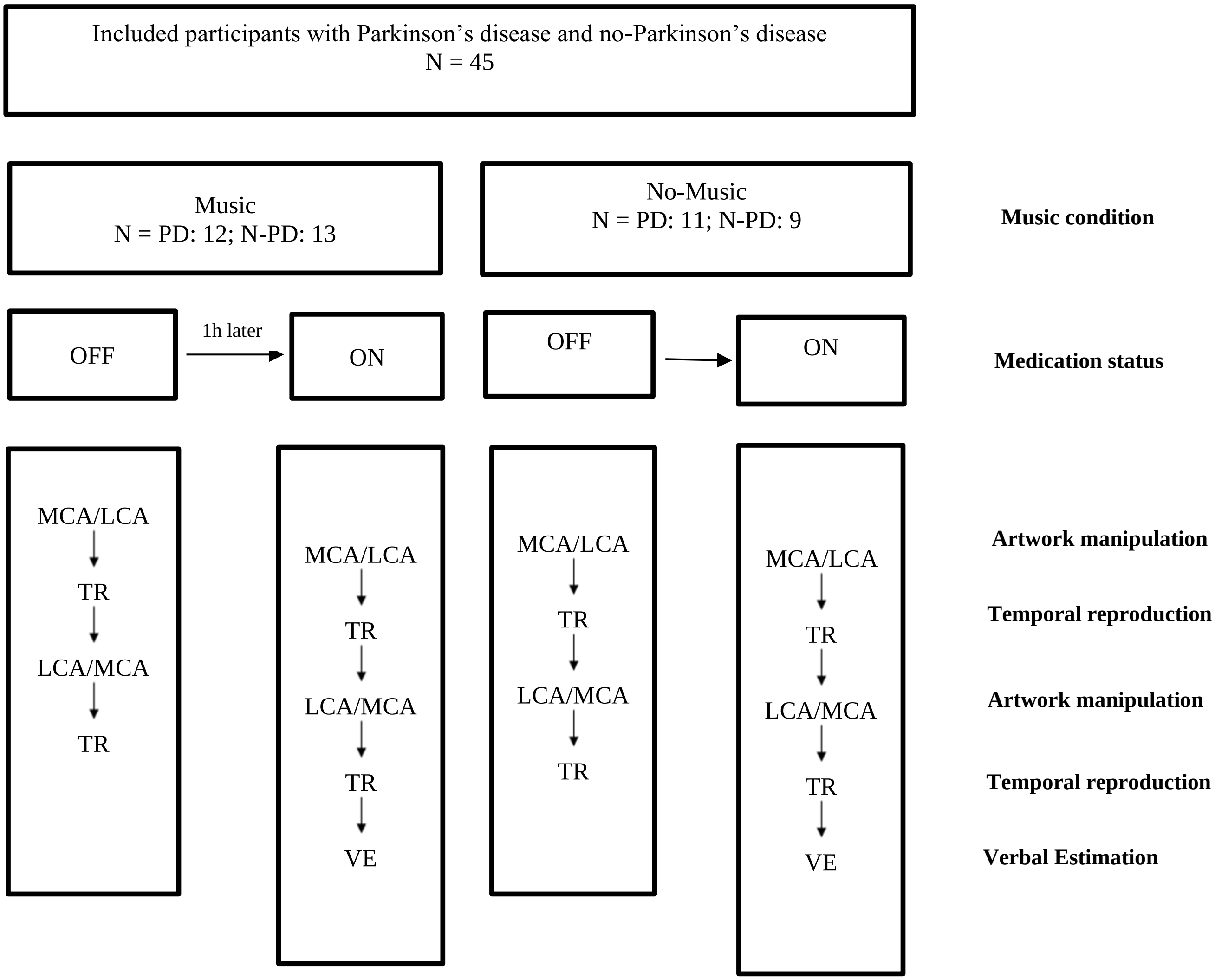
Participants sat in a chair positioned in front of the bulkhead and were instructed to assume a comfortable position so that their hands reached the center of the compartment. The task consisted of manipulating one artwork at a time, which is MCA and LCA (the order of presentation of each artwork was distribute randomly), in the presence or absence of music. The task was explained verbally by the examiner. The duration of artwork manipulation was the music presentation time (45s). In the case of the non-music condition, the manipulation time was mark by two beeps, spaced by an interval of 45s, the same duration as the condition with music.

PD patients were evaluated in both medication conditions (OFF and ON) on the same day. The design of the experiment allowed the test to be performed in a single day for each participant, thus reducing the test stress associated with multiple testing sessions (Sacrey et al., 2011).

When on OFF medication, the participants manipulated one of the artworks for a period of 45s, immediately after, they reproduced the manipulation time through a button connected to a computer: the button was pressed to start the reproduction of the time and pressed again to end reproduction. Then, the participants manipulated the other artwork (the order of presentation of the artworks was assigned randomly) and reproduced their manipulation time. When on ON medication, the same procedure was performed as when the participant was on OFF state (Figure 4). The manipulation of artworks was record for later analysis of the frequency of movements performed by the participants.

Figure 4

Tasks of Time Perception and Manipulation of artworks



Note: PD = Participants with Parkinson's disease; N-PD = Participants without Parkinson's disease; OFF = no-medication; ON = medication; MCA = More complex artwork; LCA = Less complex artwork; TR = Temporal reproduction; EV = Verbal estimation.

At the end, the participants were asked to verbally estimate the manipulation duration of the artworks. Five semantic differential scales (7-point Likert scale) were used for participants to evaluate the artworks (Figure 5). The collative properties were*: (a) Simplex-Complex, (b)*

Irregular-Regular, (c) Few pieces-Many pieces, (d) Interesting-Uninteresting, and (e) Pleasant-Unpleasant.

Figure 5

Five semantic differential scales

What is the complexity level of the object?

Little	1	2	3	4	5	6	7	Very

What is the regularity level of the object?

Little	1	2	3	4	5	6	7	Very

Did you think that the number of pieces in the object was...

Little	1	2	3	4	5	6	7	Very

How interesting did you find the object?

Little	1	2	3	4	5	6	7	Very

How pleasant did you find the object?

Little	1	2	3	4	5	6	7	Very

4.2 Data Analyses

Data were collected from 57 participants (PD: 33; non-PD: 24), however, data from some participants were excluded from the analysis of a procedure if the participant did not feel well, could not understand the instructions, did not attend the session for the application of neuropsychological test or was an outlier. The sample sizes for the analyses of the different conditions were: temporal estimation test: PD 23, non-PD 22; manipulation categories: PD 22, non-PD 21; Neuropsychological tests: *Interlocking finger test*, *Digit span test*, *Mattis dementia rating scale* and *Boston naming test*: PD 22, non-PD 21; *Clock drawing tests* and *Verbal fluency* *tests*: PD 22, non-PD 20; *Frontal assessment battery*: PD 19, non-PD 20. The *p*-value for all analyzes was set to <0.05. The partial eta squared effect size ($\eta^2 p$) was applied for all analyses, which can be interpreted: 0.01 = small effect; 0.06 = medium effect; 0.14 = large effect. The table 1 illustrated the data.

Table 1

Mean and standard deviation (SD) of the participants characteristics with and without Parkinson's disease.

	PD participants	**Non-PD participants**	***P***
Number of participants	23 participants (19 male; 4 female)	22 participants (9 male; 13 female)	
Mean of age (sd)	55.30±6.9	56.41±9.5	.659
Education (year±sd)	9.6±4.8	10±4.1	.722
UPDRS-III			
OFF	38.49±3		.001
ON	18.64±2.3		
Mattis	137±1.25	139±1.31	.39

Note: PD = patients with Parkinson's disease; non-PD = participants without Parkinson's disease; SD = standard deviation; UPDRS-III = Unified Parkinson's disease rating scale – part III; OFF = PD patient no medicated; ON = PD patient medicated: Mattis = Mattis dementia scale.

Temporal tests: temporal reproduction (TR) and verbal temporal estimation (VE)

To identify the accuracy of time reproduction (TR) and verbal temporal estimation (VE), the raw value of TR and the VE was subtract from the manipulation duration, that, i.e., 45s: raw value of TR/VE - 45 = temporal estimate. Thus, if the result was 0 (zero), the temporal estimate was exactly the manipulation duration; if the result was negative, it indicated underestimation;

and if the result was positive, it denoted overestimation. The results found were submit to statistical analysis.

For temporal reproduction, a repeated measures ANOVA was perform using the mixed model with group (PD or non-PD) and condition (music or non-music) as independent variables, and two dependent variables: medication (OFF/ON or “OFF/ON”-yoked), and artwork (less or more complex).

For the verbal time estimation, repeated measures ANOVA was applied using the mixed model with group (PD or non-PD) and condition (music or non-music) as the independent factors between subjects and artwork (less or more complex) as within subjects’ factors.

If the patients’ medication status affected performance, this might not appear as a simple medication effect, as the “medication status” for non-PD participants does not indicate different treatments. The same was true for any interaction which the difference of “OFF/ON status” alone was involved, e.g., when data from non-PD participants were analyzed separately. However, if the patients’ medication status affected their performance, this was considered through the manifestation of the interaction between the medication and the group, so that the medication effects were significant for the PD group.

Categories of Stimulus Manipulation

The manipulation of artworks was recorded, and the movements performed by the participants were analyzed using the *EthoLog 2.2 program* (Ottoni, 2000), a tool that aids in observing behavior, registering its sequence, frequency, and duration. Movements were analyzed according to the manipulation categories used by Motta et al. (2019), who analyzed the manipulation of artworks in PD patients. Thus, the movement of hands and fingers during exploration was analyzed. Three categories were considered: (a) Touch, (b) Release the artwork and (c) Move. The Touch category referred to touch performed with the palm and/or fingers. The Release category was related to when the artwork was release by the participant with no contact between artwork and hands. The Move category indicated the movement of the plates performed with the palm and fingers.

A repeated measures ANOVA was perform using the mixed model with group (PD or non-PD) and condition (music or non-music) as independent variables, and two dependent variables: medication (OFF/ON or "OFF/ON"), and artwork (less or more complex).

Semantic Differential Scales

A mixed model repeated measures ANOVA with group (PD or non-PD) and condition (music or non-music) as the independent factors between subjects and artwork (less or more complex) as factors within subjects was applied to each one of the five semantic differential scales (complexity, regularity, number of pieces, interesting and pleasing).

Neuropsychologic Tests

For the analysis of the neuropsychologic tests *[Interlocking finger test (IFT), Digit Spam test (DST), Mattis dementia rating scale (MDRS), Clock drawing test (CDT), Verbal fluency test (VFT), Boston naming test (BNT)* and *Frontal assessment battery (FAB)]* a MANOVA (two-way) were applied with the independent factors group (PD or no-PD) and condition (music or non-music).

Correlations

To examine the relationships between time estimates and cognitive functions, Pearson correlations tests were calculated between temporal estimates (TR and VE) and neuropsychological tests scores.

4.3 Results

To aid comprehensibility, a detailed exposition of the negative results was omitted, and non-significant effects were noted.

Temporal tasks: temporal reproduction (TR) and verbal temporal estimation (VE)

For the temporal tasks, the mean of the estimates was calculated to reflect the overall pattern of over- or underestimation of the data. Describing the results, it was found for TR, PD patients and non-PD participants in both conditions (music and non-music) underestimated the manipulation duration compared to the objective time (45s), regardless of the medication status (OFF and ON) and the complexity level of the artworks (LCA and MCA). On the other hand, for VE, participants with and without PD in both music conditions (with and without music) overestimated the manipulation duration of artworks regardless of the complexity level. The Table 2 shows the mean of the time estimates of manipulation of the artworks by the participants.

Table 2

Mean and standard deviation (SD) of the temporal estimates of the manipulation duration of artworks made by the participants

Artwork	Music condition		Non-music condition	
	PD (mean±SD)	Non-PD (mean±SD)	PD (mean±SD)	Non-PD (mean±SD)
	Temporal Reproduction			
LCA	-16.5±2.8	-15.8±2.7	-17.1±2.9	-19.8±3.2
MCA	-13±3.1	-14.5±3	-16.1±3.3	-14.3±3.6
	Verbal time estimation			
LCA	11.4±9.1	2.3±8.8	9.7±9.5	20.5±10.5

MCA	19.5±12.1	10±11.7	17±12.7	37±14

Note: PD = patients with Parkinson's disease; non-PD = participants without Parkinson's disease; SD = standard deviation; LCA = Less complex artwork; MCA = More complex artwork.

Temporal Reproduction (TR). The TR of the manipulation time of the artworks was underestimate by the PD patients and non-PD participants regardless of condition (music and non-music), medication status (OFF and ON) and artworks. This result was illustrated in the Figure 6. The statistical analysis showed that the participants (PD and non-PD) had different temporal reproductions depending on the complexity level of artworks, as demonstrated by the significant effect of the artworks on the time estimation, F(1;41) = 5.68, p = 0.02, η^2p = 0.12. In fact, the MCA manipulation time was significantly less underestimated (-14.74) when compared to the LCA manipulation time (-17.29).

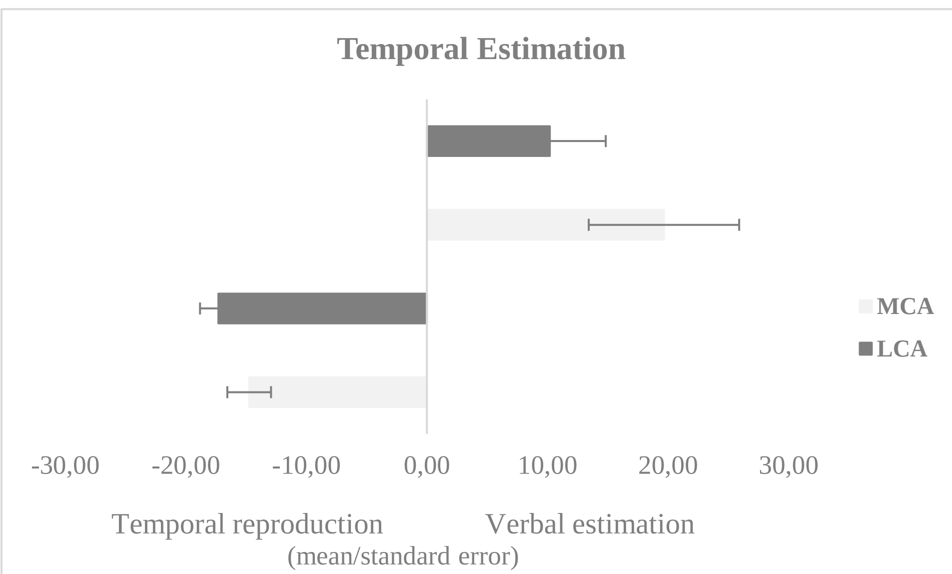
There was no significant interaction of artworks with the group, F(1;41) = 0.61, p = 0.44, η^2p = 0.01, artworks with condition, F(1;41) = 0.40, p = 0.53, η^2p = 0.01 and artworks with medication, F(1;41) = 0.007, p = 0.93, η^2p = 0.0001. There was no group effect, F(1;41) = 0.003, p = 0.96, η^2p = 0.0001, condition (music and non-music), F(1;41) = 0.32, p = 0.57, η^2p = 0.008, nor interaction, F(1;41) = 0.008, p = 0.93, η^2p = 0.0002. Furthermore, there was no significant effect of medication (OFF and ON), nor interaction of medication with group, and medication with condition.

However, there was a significant effect of the Group x Artworks x Medication status interaction: F(1;41) = 4.05, p = 0.05, η^2p = 0.09. Medication status showed to influence time estimation for PD patients. In OFF medication, patients underestimated the manipulation time of the MCA (-14) less than those estimated for the LCA (-17.45). Nonetheless, when the patients were in ON medication there was no significant difference in the estimation of manipulation time between LCA (-16.12) and MCA (-16.15). For non-PD participants there was a significant different in the estimation of the manipulation time of artworks under “OFF” and “ON” conditions. When in “OFF,” participants underestimated the manipulation duration of the MCA less (-17.33) in relation to the LCA (-18.82) – like that found for PD patients on OFF medication – when non-PD participants were in the “ON” condition the same result found in the “OFF” condition was observed (MCA: -11.47; LCA: -16.75). This result was expected, since there was no effect of drug treatment in participants without PD.

There was no effect of interactions: group x condition x medication, group x condition x artworks, and artworks x medication x condition.

Figure 6

Mean and standard error of temporal reproduction and verbal estimation of the manipulation time of artworks performed by the participants



Note: MCA = More complex artwork; LCA = Less complex artwork

Verbal Time Estimation (VE). The VE of the manipulation time of artworks was overestimate by PD patients and non-PD participants, regardless the condition (music and non-music), medication status (OFF and ON) and artworks. This result was illustrated in the Figure 5. The statistical analysis showed that the complexity level of the artworks influenced the VE of the manipulation time, as there was a significant effect of the artworks on the time estimation, F(1;43) = 12.19, $p = 0.001$, $\eta^2p = 0.22$. Participants (PD and non-PD) more overestimated the duration of MCA manipulation (20.9) than the duration of LCA manipulation (11).

There was no significant interaction of artworks with the group (PD and non-PD), and artworks with condition (music and non-music). There was no group effect, condition, nor interaction. Furthermore, there was no effect of the group x condition x artworks interaction.

Artwork's manipulation categories: Touch, Release and Move

The group was shown to be a variable that affected the frequency of all categories: Touch, F(1;37) = 11.05, $p = 0.002$, $\eta^2p = 0.23$, Release, F(1;37) = 7.77, $p = 0.008$, $\eta^2p = 0.17$, and Move, F(1;37) = 34.23, $p < 0.001$, $\eta^2p = 0.94$. PD patients performed less touching the artworks (23.9), less releasing the artworks (20.5), and had a lower movement frequency when exploring artworks (13.3) when compared to non-PD participants (frequencies of Touch: 32.9, Release: 28.6, and Move: 21.7).

In addition, there was an effect of medication on the frequency of touches, F(1;37) = 5.32, $p = 0.03$, $\eta^2p = 0.12$. PD patients performed more touches when ON medication (26.01) than when were OFF (21.9). Similar result was found for non-PD ("OFF": 32.63, "ON": 32.22). However, for non-PD participants, there was no drug intervention.

Semantic differential scale

There was no effect of group and condition, but there was a highly significant effect of artworks on the assessment of the level of complexity, F(1;42) = 41.44, $p < 0.001$, $\eta^2p = 0.509$, number of pieces, F(1;40) = 40.68, $p < 0.001$, $\eta^2p = 0.504$ and interest, F(1;40) = 7.80, $p = 0.008$,

$\eta^2p = 0.163$. There was no effect of artworks in the assessment of the level of regularity, and pleasantness. Thus, MCA was rated as more complex (5.9), with a greater number of pieces (6.1) and more interesting (5.84) compared to LCA, which thus was rated as less complex (5.9), with fewer pieces (4.5) and less interesting (4.5).

None of the interactions were significant, except the interaction between the group and the artwork for the complexity scale, $F(1;40) = 4.54$, $p = 0.04$, $\eta^2p = 0.102$, and number of pieces, $F(1;40) = 3.82$, $p = 0.05$, $\eta^2p = 0.086$. PD patients rated the MCA as having greater complexity (5.6) and a greater number of pieces (5.85) than LCA, which was rate as having a lower level of complexity (4.7), a lower number of pieces (4.73). Like the PD patients, non-PD participants showed the same pattern of evaluation of the artworks for the scales of complexity (MCA: 6.16; LCA: 4.37) and number of pieces (MCA: 6.32; LCA: 4.24).

Neuropsychologic Tests

The scores of neuropsychologic tests obtained by PD patients and non-PD participants are show in Table 2. Data analysis revealed significant differences between the two groups of participants in the Verbal Fluency Test for the semantic and phonetic dimensions. PD patients performed less than non-PD participants ($p < 0.05$).

A marginally significant difference was found between the groups of participants for the MDRS dimensions attention ($p = 0.072$) and conceptualization ($p = 0.06$), and for the Frontal Assessment Battery ($p = 0.07$), with PD patients presenting lower scores compared to non-PD participants (Table 3).

Table 3

Mean, standard deviation and significance of neuropsychological test scores to which PD patients and non-PD participants underwent

Neuropsychologic Tests		**PD patients** [Mean (SD)]	**Non-PD participants** [Mean (SD)]	***p***
IFT		3.6±0.21	3.8±0.22	.55
DST-Total		11.9±0.72	12.5±0.75	.587
	Direct order	7.2±0.41	7.2±0.43	.948
	Indirect order	4.7±0.46	5.2±0.49	.434
MDRS-Total		137±1.25	139±1.31	.266
	Attention	34.6±0.35	35.6±0.37	.072**
	Initiation	35.8±0.69	35.4±0.72	.682
	Construction	5.8±0.1	5.9±0.1	.191
	Conceptualization	36.9±0.41	38.1±0.43	.06**
	Memory	23.9±0.3	24±0.32	.752
CLOX 1		11.4±0.47	11.52±0.5	.842
CLOX 2		13.4±0.34	13.9±0.36	.302
VFT-Semantic		17.9±0.81	21.43±0.87	.006*
VFT-Phonetic		28.5±1.84	35.3±1.96	.016*
BNT		13.8±0.5	14.3±0.5	.45
FAB		14.6±0.5	15.9±0.5	.07**

Note: IFT: Interlocking Finger Test; DST: Digit Span Test; MDRS: Mattis Dementia Rating Scale; CLOX: Drawing Clock Test; VFT: Verbal Fluency Test; BNT: Boston Naming Test; FAB: Frontal Assessment Battery.
*p value < .05
**p value marginally significant

Correlations

The analysis of correlations between time estimates (TR and VE) and neuropsychological test scores revealed a significant correlation between the DST direct order and reproduction of time of manipulation of the LCA when PD patients were on OFF medication, r = 0.51, $p < 0.001$, and a negative correlation for indirect order and verbal estimation of MCA manipulation time when PD patients were on ON medication, r = -0.33, $p = 0.03$. Therefore, as the DTS direct order score increased, the manipulation duration of the LCA increased. Conversely, as the indirect order score increased, the verbal estimate of MCA exploration time decreased.

There was also a negative correlation between the CLOX 2 test score and the verbal estimation of MCA manipulation time, r = -0.32, $p = 0.04$. Another negative correlation was found between the FAB score and the verbal estimation of the MCA exploration duration, r = -0.34, $p = 0.03$. These results indicate that as the score for the CLOX 2 test increased, the verbal estimation of the LCA exploration time decreased, and as the FAB score increased, the verbal estimation of the duration of the MCA exploration decreased. Both correlations are related to when the PD patients were on ON medication.

In addition, there was a positive correlation between the Phonetic Verbal Fluency test score and the reproduction of the MCA manipulation time when PD patients were in the ON state, r = 0.32, $p = 0.04$. Which means that in the ON condition, as the Phonetic dimension score increased, the reproduction duration of the MCA exploration increased.

4.4 Discussion

The main finding of this study was that the level of complexity of the artworks showed to affect temporal estimations, that is, participants, regardless of group (PD or non-PD) and condition (music or non-music), experienced the manipulation time of the MCA different of the manipulation time of the LCA. Specifically, the reproduction of manipulation time for the MCA was less underestimated (subjective perception of lengthening of time) than it was for the LCA. The verbal estimation of the manipulation duration of the MCA was more overestimated than it was for the LCA. These results are compatible with our hypothesis about the effect of different levels of complexity of artworks on temporal perception. However, contrary to what we suppose, the complexity of the artworks did not influence the manipulation, the artworks had the same frequency of movements (touch, release and move). Furthermore, the lack of effect of music on the perception of time and on the manipulation of artworks was an unexpected finding. Also, the absence of difference in time estimates between PD patients and non-PD participants was not an expected fact.

Nonetheless, these findings replicate previous studies, which used temporal reproduction task with a simultaneous reading condition and found no differences in time estimation between PD patients and non-PD participants. All participants under-reproduced the duration (5, 14, 38s. Perbal et al., 2005; Pouthas, & Perbal, 2004). Other studies asked participants to verbally estimate the duration of 500Hz tones and found no differences in the estimation between PD patients when compared to the estimation of non-PD participants (Wearden et al., 2008; Wearden et al., 2009). In addition, Motta et al. (2019) found, in a retrospective judgment paradigm, that participants with and without PD did not differ significantly in the verbal estimation of the manipulation time of artworks with different level of complexity. However, it is important to mention that PD patients less overestimated the time then non-PD participants.

On the other hand, results found different from ours. Riesen and Schnider (2001), using the prospective judgment paradigm, asked participants to simultaneously finger tap and read aloud numbers during different time intervals (12, 24, 48s) and observed that the PD patients and non-PD participants kept the taps constant throughout the three durations and, like us, they did not find differences in the verbal estimation of PD patients when compared to non-PD participants. However, contrary to our result, their participants underestimated all durations. Likewise, another study did not observe significant differences in reproduction time between PD and non-PD participants. All participants were accurate when judging intervals of 11 and 22s, even if the reproductions of durations occurred after 5 minutes of their presentations (Honma et al., 2018), while our finding showed under-reproduction of time. Riesen and Schnider (2001) justified their results by arguing that the visual-motor task, such as tapping, did not distract attention from the passage of time. Thus, PD patients were as accurate as non-PD participants in estimating the duration of the intervals. In our study, differences were found between the groups of participants for the performance of the visual-motor task, which were evidenced by the different frequencies of the manipulation categories between the groups. However, as in the study of Riesen and Schnider (2001), there was no significant difference in the temporal estimate between PD patients and non-PD participants. On the other hand, the verbal estimation of the manipulation time of artworks was overestimate by our participants. Honma et al. (2018) considered that both PD and non-PD participants had normal memory capacity for time reproduction, being accurate in their estimates. And like Honma et al. (2018), in our study, there was no difference in temporal reproduction between participants with and without PD, however, our participants underestimated the time of manipulation of artworks. How to explain our results?

Considering that our results showed differences in the estimation of manipulation time between artworks with different levels of complexity, we assume that the complexity attributed to artworks increased the subjective perception of duration. In fact, the complexity of the artwork (collative property) was constituted as a “non-temporal” perceptual variable that seems to have affected the apparent duration.

In the field of artistic appreciation, isolated properties of stimuli affect perceptual mechanisms (Berlyne, 1958, 1963, 1974; Bueno et al., 2020). In the study by Bueno et al. (2020), modified sculptures were manipulate by healthy participants. The result showed that stimuli judged to have a greater number of pieces were also evaluated as presenting high levels of complexity, and stimuli judged to have a higher level of complexity were considered more interesting. A study in which PD patients manipulated sculptures for the desired amount of time, not having the expectation of frustrated manipulation by the end of the task externally established, verbally overestimated the manipulation time (Motta et al., 2019). In our study, the MCA, in fact, was rate as more complex, containing more pieces, and as more interesting than the LCA. This result agrees with that found by Berlyne et al. (1963) who found that the complexity of an object was a determining factor for it to be considered interesting and pleasant.

An interesting point to mentioned is that the underestimation for the reproduction of the manipulation duration of artworks in our study may be related to the perception of lesser completeness of the artwork. This is because the established time (45s) may not have been enough to meet the participants' need to better explore the stimuli. In this process, the expectation of exploration would have developed, however, the lived experience was not as expected, which would have changed the perception of the artworks and the duration perception of the exploratory behavior. This would be compatible with the *Fractal Development Expectation* model of Firmino and Bueno (2008), which argues that the perception of less completeness of a stimulus (in the authors' case, the musical tonal distance) would generate temporal underestimation due to an unmet expectation. However, this is just a conjecture, with no direct correlation with our results, as this temporal judgment model was applied to musical stimuli. In our study, the time perception refers to the manipulation time of artworks.

Furthermore, according to the processing principle (Matthews & Meck, 2016), salient properties found in a stimulus lead to the strength of its perceptual representation, as they make the experience vivid and facilitate the perception of information, which affects the extension of the apparent duration of the stimulus presentation. Thus, the evaluated collative properties modulate the strength of sensory input, allocating attention to these components and making time seem to last longer (Matthews & Meck, 2016). Our result seems to be in accordance with this principle, the greater number of pieces in the artwork, constituted as salient property, contributed to the MCA be perceive as more complex, consequently increasing the informational content extracted from the artwork and generating a more vivid experience. This would have diverted attention from the passage of time and led to the manipulation of the artwork, inducing the participants to subjectively perceive the exploration time of the MCA as longer than the exploration duration of the LCA. In addition, the multisensory nature of the task, which involved touch, motor activity, vision, and hearing, may have contributed to making perception subjectively more vivid and objectively facilitating the identification and categorization of artworks and subjectively extending the duration perception of the lived experience (Matthews & Meck, 2016).

It is important to consider that the increase in the frequency of touches by patients when in ON medication may be related to the assessment of greater complexity and interest attributed to MCA and to the absence of difference in the reproduction of the manipulation time of artworks. The higher frequency of touching the stimuli when patients were in ON medication would have altered the perception. Although, the statistical analysis of the semantic evaluations showed an interaction between group and artwork, in which patients did not show differences in the semantic evaluation of the two artworks. On the other hand, the assessment of the level of complexity of the MCA may be due to the patients' difficulty in moving, even though more touches were performed. Motta et al. (2019) suggested that the greater frequency of touches to sculptures would not have improved the quality of movement in patients in ON medication. Furthermore, the assessment of the level of complexity of the MCA may be associated with greater number of pieces, as more pieces in the artwork would have induced the perception of greater complexity. In addition, the greater frequency of touches in the ON condition by PD patients may have eliminated the difference between the reproductions of the manipulation duration of the artworks, difference that was observe when patients judged the time in the OFF condition.

In our study, cognitive processes were analyzed. The scores obtained by participants in the tests showed that PD patients had lower scores than non-PD participants. However, these scores seem not to have affected the temporal estimates, as there was no significant difference in the temporal judgments between the groups of participants. These results agree with previous data, which showed no difference between PD patients and healthy participants for the accuracy of the reproduction task, with both groups reproducing shorter durations, although PD patients had lower scores in a battery of neuropsychological tests (Perbal et al., 2005). Thus, our findings may suggest that cognitive factors, such as those evaluated in our study, may be intact, and the psychomotor slowness (confirmed by the lesser exploration of the artworks) could justify the impaired performance in the tests and the absence of difference in the patients' perception of time. On the other hand, our results do not mean that cognitive processes are not involved in the subjective estimation of time, on the contrary, duration judgments were correlated with scores of memory test (*DST* and *VFT*), visual-spatial perception and constructive perception (*CLOX*) and executive function (*FAB*), regardless of whether the participants have PD or not. These findings are corroborated by studies that found a relationship between time perception and cognitive functions, such as attention demands (Block et al., 2010; Motta et al., 2019) of memory (Koch et al., 2008; Malapani et al., 1998; Malapani et al., 2002) and of executive functions (Dušek et al., 2012; Jones & Jahanshahi, 2014).

Notably, our findings showed that participants with shorter reproductions of time and longer verbal estimations of time were those with lower scores on tests that assessed memory (DST). This occurred probably because in temporal reproduction the target duration would be store in working memory and episodic memory, and under-reproduction would occur because of the difficulty in retrieving information from memory. In the case of verbal estimation of time, the temporal judgments were performed only at the end of the experiment, that is, after the participants had manipulated the artworks under the OFF and ON medication. This time interval between experience and estimation would have lengthened the perception of the passage of time. These findings would agree with studies that pointed to the central role of memory for subjective temporal perception, (Jones & Jahanshahi, 2014; Matell & Meck, 2004; Matthews & Meck, 2016) and, also, with the finding by Perbal et al. (2005) which showed that participants with and without PD who had shorter reproductions of durations were those with lower scores on tests that assessed late recall (Perbal et al., 2005). In addition, in our study, the participants who presented longer verbal estimation of time were those who presented lower scores in tests that analyzed executive function and visual-spatial and constructive perception (Clox, FAB and Verbal fluency). Considering that the dual task used in our study (simultaneously paying attention to time and manipulating an object) involves executive processes, such as planning, attention, and processing speed, as well as to visual-spatial and constructive perception, it makes sense that these cognitive aspects are related to the results found. Parker et al. (2013) argued that temporal perception can be a type of executive function. Studies have shown that, associated with executive dysfunction, PD patients have consistently shown impairment in temporal judgment tasks (Artieda et al., 1992; Jahanshahi et al., 2010; Jones et al., 2008; Malapani et al., 1998; Malapani et al., 2002; Merchant et al., 2008).

The correlations found between cognitive functions and the perception of time of manipulation of artworks are in line with the findings that showed the relationship between temporal information processing and neural structures responsible for cognition (Dušek et al., 2012; Jones et al., 2008; Koch et al., 2008; Wearden et al., 2009; Wojtecki et al., 2011). Studies with PD patients showed that the BG and the dopaminergic system appear as critical brain structures involved in processing temporal information and converge in declaring that the cortico-thalamic-striatal-cortical circuit is frequently activated in tasks of perception of durations (Honma et al., 2018; Koch et al., 2005; Koch et al., 2008; Koch, Olivieri et al., 2004; Torta et al., 2010). Wojtecki et al. (2011) observed that bilateral stimulation via STN-DBS improved temporal reproduction in PD patients. In a study conducted by Koch, Oliveri et al. (2004) repetitive transcranial magnetic stimulation (rTMS) over the right lateral dorsum prefrontal cortex improved the reproduction of time of the PD patients. Dušek et al. (2012) pointed out the precuneus as a cortical portion connected to the judgment of time. Furthermore, there is evidence that dopamine neurotransmitters can allow compensatory activation in neurobiological structures and networks that would lead to an improvement in cognitive performance, consequently leading to more accurate time perception. (Malapani et al., 1998; Malapani et al., 2002; Perbal et al., 2005; Riesen & Schnider, 2001).

Consistent with the significant role of the BG and the dopaminergic system for the time perception (Jones et al., 2008; Mitchell et al., 2018), our findings, showed an effect of dopaminergic medication on the duration judgment. PD patients on OFF medication underestimated the reproduction of the MCA manipulation time less than the LCA manipulation time. On the other hand, this difference between the temporal reproduction of both artworks disappeared when patients were on ON medication. The sub-reproduction was the same for the duration of the manipulation of the two artworks. Non-PD participants had comparable results to PD patients in the OFF condition. Thus, PD patients without dopaminergic medication seem had a sense of time that resembled the performance of non-PD participants. The results further suggest that the proposition that increased dopaminergic function leads to improved performance in temporal tasks is not suitable for all temporal processing tasks (Jones et al., 2008). Koch et al. (2008) suggested that non-dopaminergic neurotransmission, such as the cholinergic, noradrenergic, and serotonergic systems, may play a relevant role in the modulation of certain cognitive processes in PD. Another assumption made by Wearden et al. (2009), is that the drug status of PD patients may not be a dependable guide to know whether they differ from non-PD participants in temporal tasks. In their study, PD patients had shorter verbal duration estimates (325-1.225ms) than non-PD participants in trials in which a tone (500Hz) was preceded by 3s of 5Hz clicks or presented without clicks. The results showed that clicks had marked effects on temporal estimates for both PD and non-PD participants. Particularly for PD patients this effect was not medication dependent. Furthermore, Dušek et al. (2012), in a study using fMRI, did not observe differences between ON and OFF conditions of the PD patients in areas of the brain previously connected to time perception. The only difference observed was the reduced deactivation of the precuneus during temporal reproduction in the ON condition. The authors argued that the finding was not a non-specific effect of dopamine, but a task-specific one, as that reduced deactivation of the precuneus occurred only during the reproduction phase, but not during the coding phase. Jones et al. (2008) found no difference between medically PD and non-PD participants in the temporal reproduction of auditory stimuli. The authors hypothesized that a *dopamine overdose* could explain the result. In this phenomenon, while areas within the BG that would have the most depleted dopamine levels in PD benefit from dopaminergic medication, other parts with less dopamine depletion suffer from the elevated level of the neurotransmitter, thus affecting the perception of time. We assume that for the task proposed in our study, our findings may indicate that dopamine depletion when PD patients were on OFF medication may have been supplement by non-dopaminergic systems (Meck, 2002a, 2002b). When PD patients were on ON medication, an effect like that of *dopamine overdose* (Jones et al., 2008) may have occurred, that is, high levels of dopamine in regions with less reduction dopaminergic would have impaired processing of temporal information.

Another hypothesis to explain our results would be that PD patients presented different stimulus perception, difference in the exploratory behavior and in the time perception when on ON medication compared to when OFF medication due to the dopaminergic medication have changed the exploratory motor behavior of the patients, since a higher frequency of touching the artworks was observed when the patients were on ON medication. Therefore, the integration between the information input from the cognitive and motor systems and environmental components may have been modify by the effect of the medication, thus eliminating the distortion of the perception of manipulation time between the LCA and MCA.

Regarding the absence of the music effect on the time perception of PD patients found in our study, the literature found did not show the use of music as an auditory stimulus in studies with PD patients in tasks of evaluation of durations. The studies found that used auditory stimuli, used tones to start and end the durations to-be-estimated, and found no differences between PD patients (regardless of the medication status) and non-PD participants in the verbal estimation of time (Wearden et al., 2008) and in temporal reproduction (Jones et al., 2008). Another study, already mentioned, used 3s of clicks before the interval to be timed and no differences were found in temporal reproduction between PD patients on OFF and ON medication, and between patients and non-PD participants (Wearden et al., 2009). In another study, PD patients with STN-DBS judged the duration of intervals of 5 and 15s, separated by two tones, and alteration of the time perception were attributed to the level of stimulation of the STN-DBS (Wojtecki et al., 2011).

Furthermore, our results did not show difference between groups for the performance of motor activity in the presence and absence of music. Other studies that used music with (Ma et al., 2009) and without (Sacrey et al., 2009; Sacrey et al., 2011) RAS found no difference in motor action (reach-to-grasp task) of PD patients. However, music has been showing to improve movement in the finger tapping task (Horin et al., 2020; Rose et al., 2019). This suggests that, although music may have a strong beat, this may not be enough to affect PD patients' perception of time and the movement of their upper limbs. The type of auditory stimulus may be important for its degree of interference in the motor activity of the arms, hands, and fingers of PD patients. Studies that used music to alter the motor behavior of PD patients highlighted that the failure of the music effect may be due to the beat frequency (Horin et al., 2020; Ma et al., 2009; Rose et al., 2019) , to collative properties (Rose et al., 2019), to the type of motor activity (Horin et al., 2020; Ma et al., 2009; Sacrey et al., 2009; Sacrey et al., 2011) and its ability to affect cognitive and perceptual functions (Fernandez-Del-Olmo et al., 2013; Gueye et al., 1998; Nowak et al., 2006; Vercruysse et al., 2012). In addition, we propose three more factors: (a) the possibility that the time interval listening to music exerts a direct influence on its effect on the movement. Music with durations of seconds would not produce such effects; (b) in an experimental study, the participant is subjected to a controlled condition that possibly interferes with the way in which the participant experiences and perceives the experience. Listening to music in an experimental environment is perceive differently than listening to the same music in a familiar environment; (c and the subject's level of engagement in music appreciation.

We chose the music used in this study due to the salient rhythm. However, its pace does not seem to have affected the time perception of the participants, including their movements. Ma et al. (2009) found a similar result to ours when using marching music as an auditory stimulus during the performance of a motor task by PD patients. The authors presented some reasons for the non-significant effect of music: (a) the distraction effect of music on the motor task may have been offset by the facilitating effect of the music's rhythm; (b) the participants would have listened to the musical excerpt globally or holistically (without focusing attention on any particular musical component), this would have imposed less demand for attention; and (c) when participants were asked to ignore auditory stimuli, their performance in the motor task was better than when they were asked to listen to the sound stimulus. This would have improved conscious movement control for PD patients.

These factors pointed out by Ma et al. (2009) may have occurred in our study, however, it is noteworthy that although the participants were not instructed to pay attention to the music, the verbal instruction superimposed on the music emphasized the maintenance of movement, which may have induced the participants to allocate the attention to manipulating artworks and ignoring music. Ringenbach et al. (2011) found an improvement in the performance of a bimanual motor task performed by PD patients when they followed external cues. The authors investigated the performance of the upper limb of PD patients through three types of cues: verbal instruction, auditory stimulus, and visual stimulus. The results showed that, although the patients presented movement alterations when compared to non-PD participants, the verbal and auditory stimuli led to an improvement in the task performance when compared to the visual stimulus. The conclusion of the study was that the benefit of auditory stimuli (including verbal instruction) may be related to reduced attention demand and greater kinematic focus.

Therefore, the effect of the music may have suffered interference from the verbal command, which called attention to the movement and, consequently, to the collage properties of the artworks. This would have influenced PD and non-PD participants equally, leading to the absence of significant effect of music on the motor behavior and time perception regardless of whether patients on OFF and ON medication. Furthermore, it would explain the differences found between the MCA and LCA related to the collative properties and the difference between the subjective perception of the time of manipulation of the artworks. However, it is important to emphasize that, although music has not improved the bimanual motor activity of PD patients, it has not impaired the performance of their motor actions either.

Limitations of our study were: the absence of the application of a semantic differential scale on the collative properties of the music used, including verbal instruction. We suggest that future investigations evaluate these aspects to verify if musical properties can affect the temporal perception and bimanual motor activity of PD patients; The non-randomization of the medication status to perform the task may have been a factor that affected the results found. In this sense, randomizing the drug condition to perform the task can lead to different findings, the small sample size. In our context, significantly part of the patients undergoing treatment have types of impairment that go beyond the clinical condition, making it difficult for the sample to be larger.

However, our findings show that the time perception is a complex phenomenon, in which multiple factors are involved. Although the BG and the dopaminergic system are considered essential for temporal processing, dysfunctions in these neural structures do not always seem to impair the judgment of durations. As for the use of music as a strategy to improve cognitive functions related to time perception and motor functions of the upper limbs of PD patients, further research is need. We suggest that different auditory stimuli with different collative properties are employed to examine their effects on PD patients, and that experimental designs try to get as close as possible to an ecological approach, enabling the music to be perform for a longer time in an environment prepared for listening to music.

In conclusion, our results showed a clear influence of the level of complexity of the artworks on the time perception and motor activity in the upper limbs of PD patients. Effect that was independent of dopaminergic medication and the presence of music.

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