PRDOA 11 (2024) 100277

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.sciencedirect.com/journal/clinical-parkinsonism-and-related-disorders

Coupling neurologic music therapy with immersive virtual reality to improve executive functions in individuals with Parkinson's disease: A Quasi-Randomized Clinical Trial

Federica Impellizzeri [a], Maria Grazia Maggio [a,*], Paolo De Pasquale [a], Mirjam Bonanno [a], Lilla Bonanno [a], Rosaria De Luca [a], Giuseppe Paladina [a], Angela Alibrandi [b], Demetrio Milardi [c], Michael Thaut [d], Corene Hurt [d], Angelo Quartarone [a], Rocco Salvatore Calabrò [a]

[a] *IRCCS Centro Neurolesi Bonino Pulejo, 98124 Messina, Italy*
[b] *Department of Economics, Unit of Statistical and Mathematical Sciences, University of Messina, Messina, Italy*
[c] *Department of Biomedical, Dental and Morphological and Functional Imaging Sciences, University of Messina, Messina, Italy*
[d] *Music and Health Science Research Collaboratory, Faculty of Music, Faculty of Medicine, Institute of Medical Sciences and Rehabilitation Science Institute, University of Toronto, Toronto, ON, Canada*

ARTICLE INFO

Keywords:
Neurologic Music Therapy (NMT)
Computer-Assisted Rehabilitation Environment (CAREN)
Parkinson's disease (PD)
Executive Functions (EF)

ABSTRACT

Introduction: Parkinson's disease (PD) is one the most common neurodegenerative movement disorder, leading to motor and non-motor symptoms, including deficits in executive functions (EF), memory, visuospatial abilities, and psychomotor speed. Current treatments are primarily symptomatic, involving pharmacological, surgical strategies. Neurologic Music Therapy (NMT) has gained recognition for its effectiveness in neurorehabilitation of PD patients and improving motor and cognitive domains, such as EF. This study combines NMT with the virtual reality (VR) platform Computer-Assisted Rehabilitation Environment (CAREN), offering customizable environments for rhythmic cue practice to provide an innovative approach to Parkinson's rehabilitation.

Methods: In our single-blind quasi-randomized controlled trial, forty patients were assigned to either an experimental group (EG = 20) or a control group (CG = 20). Both groups underwent two months of training with CAREN scenarios (three times a week for 24 sessions). The experimental group additionally received NMT applied to the selected scenarios. Participants were evaluated by a neuropsychologist at baseline and immediately after training.

Results: Intra-group analysis showed significant improvements in the EG for MOCA ($p = 0.007$), FAB ($p = 0.008$), Stroop Error ($p = 0.003$), Stroop Time ($p < 0.001$), and Visual Search ($p < 0.001$). The CG showed a significant difference only in Stroop Error ($p = 0.02$).

Conclusions: This pilot study is the first to combine NMT with CAREN in PD patients. Our findings suggest that NMT, within an immersive VR environment, effectively improves cognitive and EF in PD. Music structured within NMT techniques, coupled with advanced audio-visual feedback from VR, offers an innovative and potentially more effective approach for managing cognitive and executive deficits associated with PD.

1. Introduction

PD is the most common neurodegenerative movement disorder with a prevalence of about 1–2 % in the older population. It has been estimated that about 5 % of all PD patients are younger than 50 years, while about 70 % are older than 65 years [1]. This progressive neurodegenerative disorder leads to motor and non-motor symptoms, which negatively affect the patient's quality of life [2]. The most common non-motor symptoms include cognitive disorders, with various severities up to dementia [3]. It has been estimated that Mild Cognitive Impairment (MCI) can be found in 25 % of newly diagnosed PD patients without dementia [3,4]. In particular, deficits in executive functions (EF), memory, visuospatial abilities, and psychomotor speed are the most encountered cognitive disorders. Early detection and treatment of cognitive disorders are of higher importance in PD, as these symptoms can affect the individual's functional abilities and daily living skills [5].

* Corresponding author at: IRCCS Centro Neurolesi "Bonino-Pulejo", S.S. 113, Contrada Casazza, 98124 Messina, Italy.
E-mail address: mariagrazia.maggio@irccsme.it (M.G. Maggio).

https://doi.org/10.1016/j.prdoa.2024.100277
Received 9 August 2024; Received in revised form 9 October 2024; Accepted 19 October 2024
Available online 21 October 2024

Despite their importance, the rehabilitation of cognitive disorders in PD is often neglected due to the healthcare system's predominant focus on motor disturbances. Nowadays the treatment of both motor and non-motor symptoms is based on "symptomatic" therapy, which benefits from pharmacological, surgical, and non-pharmacological strategies. Regarding these latter, in recent decades there has been a growing attention to rehabilitation through music [6]. Music, considered a healing art since antiquity, offers a variety of benefits, including mood enhancement, increased work capacity, pain relief, and stress reduction [7]. In a rehabilitation context, music therapy consists of non-verbal communicative techniques used to assist individuals in expressing, containing, and modifying emotions, cognitions, and dysfunctional attitudes resulting from PD [8].By employing music as a therapeutic medium, individuals with PD can explore and navigate their emotional and cognitive experiences in a supportive and non-judgmental environment [9].Music based intervention (MBI) sessions may involve activities such as listening to music, creating music, and engaging in rhythmic exercises, all of which aim to enhance emotional regulation, cognitive functioning, language, gait and motor abilities and overall well-being for individuals living with PD [10–14].

The therapeutic approach known as "Neurologic Music Therapy" (NMT), established in the US two decades ago, has gained worldwide recognition for its effectiveness in neurorehabilitation [15]. NMT encompasses three sensorimotor techniques, all aimed at improving motor skills: Rhythmic Auditory Stimulation (RAS), focuses on fostering rhythmic motor activity, particularly in walking, using rhythmic auditory cues, metronome or footstep sounds to guide patient movements [16,17]; Patterned Sensory Enhancement (PSE), aims to enhance movements associated with daily activities, utilizing various musical elements (pitch, dynamics, harmony, meter, and rhythm) to organize movement patterns in time and space [18,19]; Therapeutic Instrumental Music Performance (TIMP), involves using musical instruments to simulate and facilitate functional movements helping to improve range of motion, limb coordination, postural control, dexterity, body perception, and sensation [20]. Furthermore, NMT promotes the well-being of people suffering from PD, with positive effects also on cognitive domains, such as EF. Indeed, Bella et al. suggested that NMT benefits could depend on patients' perceptual and sensorimotor abilities, sustained by residual neural activities and alternative functional pathways [21]. The use of RAS activates brain networks involved in motor control and rhythm maintenance, enhancing cognitive abilities [22]. Murgia et al. highlighted the effectiveness of rehabilitation programs integrated with ecological and artificial RAS in improving patients' abilities [11]. From this perspective, it could be useful to combine NMT techniques with virtual reality (VR) platforms, such as the computer-assisted Rehabilitation Environment (CAREN – Motekforce Link; Amsterdam, The Netherlands), as they offer customizable environments in which patients can practice following rhythmic cues, improving the effectiveness of treatment and providing an innovative approach to Parkinson's rehabilitation. In previous studies, the potential of the CAREN system in improving patient recovery has been widely highlighted, thanks to its advanced visual and audio feedback. In fact, benefits on improving motor performance in PD were highlighted by Calabrò et al., in a study conducted on CAREN device in 2020 [23]. Combining RAS with VR could lead to several significant benefits, as highlighted by Ashoori et al. [24]. Immersive VR could be used to create a virtual environment with rhythmic feedback facilitating the synchronization of patient movements with virtually generated sounds or visual rhythms. Furthermore, interaction with the CAREN virtual environment offers a unique opportunity to improve patients' skills, encouraging them to follow the proposed rhythms and movements, thus helping to strengthen their sensorimotor and perceptual abilities [25]. According to the findings of Gangemi et al., VR can activate neural circuits involved in movement processing and rhythm maintenance, stimulating brain networks associated with motor control and sensory integration[26] Finally, customizing CAREN to patients' individual needs allows them to exercise at an appropriate level of difficulty, promoting active engagement in therapy and improving overall effectiveness of treatment, cognitive functions and coping strategies [27].

These studies have shown that both NMT and VR can have positive effects on patients with Parkinson's disease, improving aspects such as motor coordination, balance, walking speed, and cognitive functions. VR, in particular, can provide an immersive and motivating environment that can enhance engagement and the effectiveness of therapy.

Despite growing interest, studies combining these two therapeutic modalities and exploring how music and virtual environments interact to stimulate neuroplasticity and improve cognitive functions, are still scarce. For this reason, we conducted an exploratory study to evaluate the effectiveness of combining NMT techniques with the CAREN in improving cognitive functions and EF of PD patients.

2. Material and methods

2.1. Trial design

The pilot study was a single-blind quasi-randomized controlled trial aimed to investigate the influence of NMT applied in a virtual environment, i.e. CAREN, on cognition and EF in patients with PD. It was conducted in accordance with the Declaration of Helsinki and was approved by the Local Ethical Committee (IRCCS-ME-23/2022). Each patient was adequately informed about the study, and offered their collaboration and signed a written consent.

2.2. Participants

Patients attending either outpatient or inpatients of IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy, from February 2022 to December 2023 were invited to enter the pilot study Inclusion criteria were: i) diagnosis of PD according to the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease [28]; ii) age between 40 and 80 years; iii) at least 5 years of schooling (Primary School); iv) Hoehn and Yahr stage < 2.5; and v) absence of disabling sensory alterations. The exclusion criteria were age > 85 years and the presence of severe medical and psychiatric illness potentially interfering with the training.

For the enrolment procedures, see the flow diagram (Fig. 1). Forty patients were randomly assigned to one of 2 groups, with twenty allocated to the experimental group (EG; n = 20) and the other twenty to receive standard treatments, forming the control group (CG; n = 20), based on the order of recruitment (in order to meet the criteria for a quasi-randomized study). For a more detailed description of the sample,

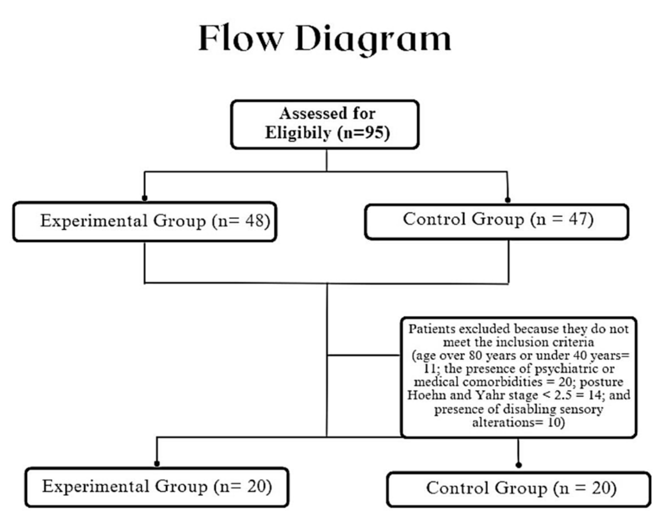

Fig. 1. Flow diagram.

see Table 1.

CG received a two-month training with CAREN selected scenarios three times a week, for a total of 24 sessions, while EG went through the same amount of training sessions with the NMT programme applied to selected scenarios. All interventions took place in a dedicated virtual reality rehabilitation room equipped with the CAREN platform at the IRCCS Centro Neurolesi Bonino-Pulejo, a clinical hospital setting with a dedicated research unit. Sessions were scheduled three times per week (for a total of 8 weeks), considering patients' other therapeutic and pharmacological commitments, with efforts to maintain a fixed schedule except in cases of medical or scheduling needs. Patients were conducted from their hospital wards to the rehabilitation room and back after each session. During the sessions, patients were positioned on the CAREN platform to perform the training. Outside the patient's 180-degree screen view, a trained NMT therapist played live rhythmic music in sync with the scenarios.

2.3. Main outcomes measures

Each participant was evaluated by a trained neuropsychologist before (baseline: T0) and immediately after the end of the training (T1). The clinical assessors (who were different from the neuropsychologist who performed the training), and the statisticians were blinded to group allocation. The neuropsychological battery included: the Montreal Cognitive Assessment (MoCA) [29] which evaluates various cognitive domains including visuospatial abilities, executive functions, naming, attention and concentration, language skills, memory, and orientation. Tasks within these domains include copying a three-dimensional cube, drawing specific shapes, performing trail-making activities, generating words belonging to certain categories, and repeating sentences. It also involves tasks to assess comprehension of spoken instructions, phonemic fluency, and recalling words or short phrases. In addition, the Hamilton Rating Scale for Depression (HRSD) [30], consisting of 17 items that evaluate various symptoms associated with depression, including mood, feelings of guilt, suicide ideation, sleep disturbances, appetite changes, and psychomotor agitation or retardation. For Executive domain we used: the Frontal Assessment Battery (FAB) [31], a neuropsychological tool, which consists of six subtests that evaluate different aspects of frontal lobe function. These subtests include assessing abstract reasoning and conceptualization, verbal fluency and cognitive flexibility, motor programming and sequencing abilities, inhibitory control and task switching, response inhibition, and the ability to inhibit automatic responses. In addition, the Stroop Test [32], designed to measure inhibition and inhibitory control, as well as cognitive flexibility, attention, and processing speed, was also administered. During the test, participants are presented with three tasks. First, they're presented with a list of colour words (e.g., red, blue, green) printed in black ink and are instructed to read each word aloud quickly; then, they're asked to name the colours of circles as quickly as possible. The third and critical part of the test involves presenting participants with colour words printed in incongruent ink colours. For instance, the word "red" might be printed in blue ink. Participants are instructed to name the ink colour of each word while ignoring the actual word itself. This creates interference because the automatic response is to read the word, conflicting with the task of naming the ink colour. Performance on this task reflects one's ability to inhibit automatic responses and focus on relevant information, indicating cognitive flexibility and executive functioning.

Lastly, the Visual Search test has been administered to investigate various aspects of visual attention, such as information processing speed, capacity for maintenance and sustained attention, and the interaction between working memory and visuo-attentive processes. Participants are required to identify specific target items among a set of distractors [33]. Improvements in performance on this test, demonstrated by higher score, indicate that the participants may have enhanced their ability to process relevant visual information more efficiently and maintain focus.

Table 1
Socio-demographic characteristics of groups.

	Experimental	Control
	Median (I-III quartile)	Median (I-III quartile)
N. Subject	20	20
Gender		
Male	14	14
Female	6	6
Age (mean ± SD)	62.35 ± 7.13	62.55 ± 9.59
Education (mean ± SD)	11.50 ± 5.82	11.75 ± 4.38

2.4. CAREN

The virtual reality rehabilitation platform used in this study was the CAREN system (Motekforce Link, Amsterdam, The Netherlands). This system comprises a 3-meter diameter motion platform capable of six degrees of freedom movements (surge-sway-heave translation and pitch-roll-yaw rotation). Positioned atop the platform is a double-banded treadmill capable of achieving speeds up to 18 m/s, with a maximum acceleration of 5 m/sˆ2. Two force plates located beneath the treadmill belts allow for the measurement of force and momentum exerted on the treadmill surfaces. Additionally, the CAREN system integrates an optical motion capture system (MoCap), incorporating 13 infrared optoelectronic cameras (Vicon Motion Systems Ltd, Oxford, UK). Platform and treadmill movements can be driven by the subject's movements recorded via either the optical MoCap system or the force plates, or by pre-programmed movements synchronized with visual stimuli and scenarios. Virtual reality immersion is facilitated by three projectors, enabling the presentation of virtual reality scenarios on a 180-degree screen positioned 3 m in front of the participant. A fourth projector is integrated to project images directly onto the treadmill surface, utilized, for example, to offer visual feedback during gait exercises. The immersive experience is further enhanced by a surround 5.1 sound system, providing comprehensive 360° audio feedback. Moreover, the system incorporates safety harnesses and handles to be grasped in the event of balance loss, ensuring participant safety.

Specifically, for this protocol, five scenarios were chosen, as shown in Table 2.

2.5. NMT procedure

The therapeutic program for the experimental group consisted of 8 weeks of individual 45-minute sessions of NMT conducted three times a week. During these sessions, participants were in an 'on' phase, representing their optimal mobility state. No prior musical knowledge or skills were required for participation in the sessions.

Each therapy session followed the same structure, involving activities within CAREN scenarios while walking on the structure treadmill. Sensorimotor NMT techniques, including RAS and TIMP, were employed. Percussion instruments such as maracas, and tambourine, along with a metronome and recorded or played rhythmic music, formed the foundation of each session. The variety of instruments in terms of size, shape, and sound provided multiple opportunities for stimulating motor activity. Music, with its key elements including pitch, dynamics, harmony, meter, tempo, and rhythm, facilitated the organization of movement in both time and space. It promoted movement fluency, muscle activation, and provided rhythmic cues to initiate and sustain the activity. Furthermore, the use of musical stimuli and musical instruments during the execution of the exercises has led not only to stimulation on a motor level, but also on the cognitive and executive functioning side, as it influenced problem-solving, planning, shifting ability, divided and sustained attention, and dual tasking. Rhythmic music, music played live by the therapist, was selected after the administering of a sound-musical anamnestic questionnaire.

Table 2
Description of caren scenarios with target skills, description of the scenarios and their training goals, lastly nmt procedure used for eg.

VR scenario	Skills	Description	Training goal	NMT procedure
Italian Alps	Gait Gait Stability Balance Motor Abilities Executive Functions Attention Visuo-spatial abilities	Challenging patient with guiding a cart through obstacle courses, traversing varying terrain gradients, and maximizing pizza assembly by gathering ingredients distributed along the pathway. Ingredients are located on the road, allowing the patient to collect them by steering the cart over them while navigating around obstacles.	Provide training sessions focusing on uphill and downhill walking, combined with an adaptability slalom task, aimed at enhancing gait stability and boosting physical capacity.	The Therapist provided live music on which they walked while retrieving the pizza ingredients A combination of techniques such as RAS and TIMP were used, along with the addition of musical instruments (maracas and tambourines) that were used concurrently with the arrival of stimuli (pizza ingredients) in addition to musical bases
Step on it	Gait Gait stability, Gait Adaptability Paced Rhythm Attention Executive Functions Visuo-spatial abilities	The participant walks along an unending pathway observed from a top view. Step length and width are assessed during gait, with cues generated in accordance with the participant's walking pattern.	The goal of this training is to challenge patients with adapting their step width and length, consequently altering step frequency in response to environmental cues. The uncluttered and straightforward virtual environment renders this application suitable for individuals with both physical and cognitive impairments.	Live accompaniment was played with the acoustic guitar while the patient walks. RAS was used to enhance rhythmic engagement and improve gait synchronization with the music
Road Encounters	Balance, Gait stability, Physical and cognitive Dual Task Attention Executive Functions Visuo-spatial abilities	The participant walks over a rough and twisting forest trail, hitting insects and birds in flight with her/his hands. Walking on the treadmill occurs either at a set speed or under the control of a self-paced algorithm.	Task the patient with engaging in a physical dual-task, involving upper extremity movements simultaneous to walking along a winding and hilly forest trail.	Live music was played and the patient, while walking to the beat of the music, had to interact with the birds and butterflies in the virtual scenario, and when it was time to hit them, they also hit the tambourine or shook the maracas provided. A combination of techniques such as RAS and TIMP were used
Rope	Gait, Gait Stability, Gait Adaptability Physical and cognitive Dual Task Attention Executive Functions Visuo-spatial abilities	The participant walks on a suspended rope bridge between towers, encountering gusts of wind that induce platform sway perturbations. While navigating the bridge, seagulls may fly past and must be evaded	This application simulates the complexity of outdoor walking within the safe and controlled environment of the treadmill system. Platform and treadmill mimic the slope and sway of the bridge, utilizing pitch and sway adjustments Anticipation training is achieved by avoiding the seagulls flying.	Live music with rhythm suitable for the pace the patient had to keep was sent. RAS was used to choose the right tempo that matches the speed of the movement you want to encourage, while TIMP technique was employed to better coordinate the patient's movements to avoid the obstacles (seagulls) along the path, using a tambourine or maracas while moving the treadmill to the left or right.
Stroop and Arithmetic	Gait, Gait Adaptability Cognitive Dual Task Attention Executive Functions	The participant walks on the treadmill, either maintaining a constant speed or under the control of a self-paced algorithm. Depending on the chosen task a coloured word or simple calculations are displayed followed by the correct answer.	Engage the patient in a cognitive dual task by incorporating the STROOP test or arithmetic exercises during gait.	Only the stroop part was selected; the patient had to walk in time with the live music played by the therapist and respond to the stimuli presented on the screen. RAS was employed to boost rhythmic involvement and enhance coordination of gait with the music

The scenarios used in combination with music and NMT techniques were particularly: “Step on it”, in which live accompaniment was played with the acoustic guitar; “Rope”, in which live rhythmic music suitable for the pace the patient had to keep was played; “Road Encounters”, where live music was played and the patient, while walking to the beat of the music, had to interact with the birds and butterflies in the virtual scenario, and when it was time to hit them, they also hit the tambourine or shook the maracas provided; “Stroop and Arithmetic”, in which only the Stroop part was selected and the patient had to walk in time with the live music played by the therapist and respond to the stimuli presented on the screen (colour words printed in incongruent ink colours that appeared on the side parts of the screen); finally, “Italian Alps”, where the patient was played a musical rhythmic base on which they walked while retrieving the pizza ingredients.

The NMT trained therapist choose to use live music because it allows direct, real-time interaction between the therapist/musician and the patient; moreover, offers greater flexibility in adapting tempo, intensity, and musical style based on the patient’s reaction and feedback, allowing for a highly responsive and dynamic therapy; furthermore, increases the patient’s emotional involvement enriching the rehabilitative experience. The choice to use live music with NMT techniques was made based on the experience of the NMT-trained therapist in combination with the CAREN scenarios. In the scenarios “Road encounters”, “Rope” and “Italian Alps”, a combination of techniques such as RAS and TIMP were used, along with the addition of musical instruments (maracas and tambourines) that were used concurrently with the arrival of stimuli. Meanwhile, in the scenarios “Stroop and Arithmetic” and “Step on it”, RAS was used.

Music was amplified by CAREN surround 5.1 sound system (jack cave connected with acoustic guitar). The volume was adjusted individually to the auditory perception of the participant. The metronome provided an additional analog auditory cue to feed the exact tempo and rhythm during exercises. In order to enhance the effect, the metronome tone was embedded into live music. Initially, the patient’s steps per minute (SPM) were measured while walking at a natural pace. Subsequently, the SPM were converted into beats per minute (BPM), considering that one step equals one beat of the metronome. The metronome was set to the patient’s natural walking rhythm, as measured during the initial assessment. Afterward, the BPM of the metronome was gradually increased by about 5–10 % over the natural rhythm (18).

2.6. Statistical analysis

The description of the groups was based on demographic and clinical variables. A nonparametric analysis was carried out because the results of the Shapiro-Wilk normality test indicated that most of the target variables were not normally distributed. The Wilcoxon signed-rank test was used to compare the clinical variables at T0 and T1 in intra-group analysis. For inter-group analysis, the Mann–Whitney *U* test was used. Analyses were performed using the open source R4.2.2 software package (R Foundation for Statistical Computer, Vienna, Austria). A 95 % confidence level was set with a 5 % alpha error. Statistical significance was set at $p < 0.05$.

3. Results

The groups were homogeneous in terms of age and education. Intra-group analysis showed a significant difference between T0 and T1 in experimental group for MOCA ($p = 0.007$), FAB ($p = 0.008$), Stroop Error ($p = 0.003$), Stroop Time ($p < 0.001$) and Visual Search ($p < 0.001$), while only a significant difference in Stroop Error ($p = 0.02$) was highlighted in the control group (Table 1). Inter-group analysis showed significant differences in Stroop Error at T0 ($p = 0.04$) and T1 ($p = 0.02$), in Stroop Time at T0 ($p = 0.02$) and in Visual Search T1 ($p = 0.006$) (Table 3).

Table 3

Neuropsychological battery of groups. *MoCA = Montreal Cognitive Assessment; HAM-D = Hamilton Rating Scale for Depression; FAB = Frontal Assessment Battery; SD = Standard Deviation.*

	Experimental	Control	p-value
	Median (I-III quartile)	Median (I-III quartile)	
MOCA T0	25 (21.75–26.00)	25 (23–27)	0.29
MOCA T1	27 (24–28.25)	25.5 (23–27.25)	0.55
p	**0.007***	0.64	
HAM-D T0	8.50 (5.75–10.50)	10 (5–12)	0.74
HAM-D T1	8 (5–10)	7 (6–14.25)	0.43
p	0.28	0.89	
FAB T0	14.85 (12.84–16.10)	16.1 (14.95–17.22)	0.08
FAB T1	16.22 (15.04–17.05)	16.25 (15.23–17.23)	0.88
p	**0.008***	0.25	
STROOP Error T0	3.18 (1.54–3.81)	0.25 (0–1.94)	0.04*
STROOP Error T1	0.67 (0.19–1.41)	0 (0.00–0.56)	0.02*
p	**0.003***	**0.02***	
STROOP Time T0	25.37 (22.74–29.45)	21.13 (17–23.88)	0.02*
STROOP Time T1	19.29 (15.82–22.12)	18.5 (13.94–25.25)	0.93
p	**<0.001***	0.33	
Visual Search T0	37.90 (31.86–40.85)	37.25 (29.19–41.00)	0.93
Visual Search T1	42.90 (40.68–46.84)	38.25 (30.25–42.00)	0.006*
p	**0.0002***	0.52	

4. Discussion

To the best of our knowledge, this is the first pilot study of NMT combined with CAREN environment in patients with PD. Indeed, our findings showed significant improvements in executive and global cognitive function in the experimental group, particularly in the Stroop and Visual Search tests. These results highlighted that immersive VR combined with rhythmic musical stimuli can be an effective tool for improving cognitive function, with regards to EF and attention abilities in patients with PD. Being a multisensory experience, VR combined with music therapy can engage various brain regions and networks relevant to both motor and cognitive processes [34]. Then, the improvement of motor and gait disturbances in patients with PD could result from a potentiation/bypass of the altered internal timing system linked to disturbances in the basal ganglia (BG), as highlighted by various authors [16,35,36]. BG play a critical role not only in motor control but also in various cognitive functions, including working memory, attention, and EF [36–38]. In the same way, PD neurophysiological impairments include a disruption of the basal ganglia-thalamocortical (BGTC) network [21]. Generally, the BGTC network is crucial for the intrinsic evaluation of temporal intervals and for initiating and maintaining actions. In the context of PD, rhythmic auditory stimuli, such as metronome tones or music with embedded beats, can help patients compensate for their timing deficits by engaging the Cortico-Thalamo-Cortical (CTC) network, which is responsible for the pre-attentive encoding of event-based temporal structures and for matching movements to external cues [39]. A specific therapeutic technique within NMT, RAS, has been used as an alternative, nonpharmacological treatment in gait training for PD patients increasing stride length and velocity [17]. RAS, providing a regular and predictable temporal structure, may help compensate for these deficits through motor neural entraining improving the synchronization of neuronal activity across brain regions. In particular, the motor system synchronizes with the rhythmic patterns of music, and this could enhance the learning and execution of motor skills by providing a stable temporal framework [22,40]. In addition, it could facilitate the allocation of attentional resources, making it easier for patients to focus and process information. Indeed, rhythmic cues can serve as an external scaffold, supporting the timing of cognitive operations, improving the efficiency of cognitive processing and stabilizing neural networks that are otherwise disrupted by BG lesions [41]. This could lead to improved coherence and communication within and between others brain networks like the BGTC network [41,42] and the CTC circuit [21]. Reinforcing the CTC network through RAS during gait training allows PD patients to predict temporal events in a better manner [43]. This temporal predictability aids in stabilizing their movements by synchronizing their actions to the beat structure provided by RAS. Therefore, rehabilitation incorporating rhythmic auditory cues and the concurrent execution of rhythmic movements (e.g., playing percussion, piano, clapping, walking) engages visual, auditory, and motor information processing within the fronto-temporo-parietal regions (FTP), that are components of the putative human mirror neuron system. This network likely facilitates the coupling between perceptual events (visual or auditory) and motor actions (leg, arm/hand, or vocal/articulatory actions), thus integrating cognition and perception to enhance cognitive function [44]. Indeed, regarding musical stimulation, various studies supported the efficacy of movement training synchronized with musical rhythm in stimulating the prefrontal cortex and enhancing cognitive function, particularly in healthy older adults with mild cognitive impairment (MCI). For instance, Shimizu et al. demonstrated that movement music therapy using percussion instruments significantly improved physical and frontal lobe functions in this population compared to movement training without musical rhythm [45,46]. Furthermore, Hars et al. found that older adults with MCI who participated a 6-month program of walking to piano rhythms showed notable improvements in global cognitive functioning, especially in EF [47]. According to these findings, we observed that in our PD patients, rhythm and music training could enhance various cognitive domains, including inhibitory control, attention, visuospatial functions, and EF. Our results are in line with other studies. It has been noticed that MBI are feasible improving cognitive and motor functions, visuospatial functions, language, and EF in PD patients [46,48]. Another scientific contribution is provided by Grahn & Brett who found that rhythmic auditory cues activate the BG, aiding motor performance in PD patients [49]. Thaut et al. reported that rhythmic music training leads to reorganization and increased activity in the cerebellum and motor cortex [50]. Furthermore, Boso et al. demonstrated that MBI can increase activation of the prefrontal cortex, enhancing EF in PD patients [51]. The prefrontal cortex is essential for planning, decision-making, and feedback-based behavioural adaptation, which are integral to the executive and decision-making process [52–54]. Indeed, Herholz et al. found that MBI improved working memory and verbal memory in older adults, suggesting potential benefits for PD patients [55]. In line with these findings, Levitin and Tirovolas highlighted that musical activities improve cognitive flexibility as engaging with music both in active participation – moving to the rhythm, playing an instrument, singing – or passive listening modalities. Also, it can promote attentional shifting through frequent changes in attention and task strategies [56]. Finally, musical training can have repercussions at the level of inhibitory control, as highlighted by Bugos et al. The authors demonstrated that piano training improves inhibitory control and cognitive performance in older adults, indicating a similar potential for patients with PD [57]. According to these findings, our sample showed that NMT plus VR group (EG) scored statistical significantly than CG in global cognitive functioning and EF (inhibitory control, attentive and visuo-spatial abilities, categorization, reasoning, shifting), like is shown in MoCA, FAB, STROOP and Visual Search results.

Together with the usage of music, this pilot study involved an immersive VR environment to enhance PD rehabilitation. VR training offers multisensory stimulation, such as audio-visual feedback, enabling intensive, repetitive, and task-oriented exercises that are crucial for enhancing neuroplasticity processes. This method allows PD patients to receive augmented feedback to the central nervous system through tasks performed in the virtual environment, facilitating the development of knowledge of results and knowledge of performance. These aspects are essential for motor learning and relearning specific to the training regimen that are amplified in an immersive VR environment. In fact, can led to increased audio/video feedback with awareness of one's movements and the results of the movements themselves [58]. Performance improvement is achieved when individuals can practice movements and receive feedback on the outcomes, allowing them to adjust and refine their performance to enhance results, a capability that VR significantly enhances [25]. Unlike other VR systems, CAREN provides an immersive virtual environment with a 6-degrees-of-freedom (6-DOF) platform, delivering a more realistic and dynamic scenario. Moreover, PD patients performed a VR training in a safe and controlled immersive environment. In fact, we previously demonstrated that CAREN avoid the perception of cybersickness, allowing a more enjoyable rehabilitation without reporting side-effects. This is because the 6-DOF platform is perfectly synchronised with the 180° VR screen [59].

To sum up, the use of immersive VR environment plus NMT can enhance EF and motor learning arousing common neural substrates, particularly the prefrontal cortex and the BG (52–54). This engagement of cortical and subcortical neural structures due to music and the VR environment could enhance synaptic communication between brain networks (the BGTC network and the CTC circuit) and integrate visual, auditory, and motor information within the FTP areas, thereby improving cognitive and EF.

4.1. Clinical implications and future directions

The clinical implications of combining neurological music therapy (NMT) with immersive virtual reality (VR) training are significant, particularly for improving executive function and motor learning in patients with Parkinson's disease. The positive results observed in this pilot study suggest that such interventions could lead to long-term improvements in cognitive and motor skills, promoting greater independence and quality of life for patients. Adherence to these innovative therapies may be high due to their immersive multisensory nature, which may motivate patients to actively participate in their rehabilitation. From a feasibility standpoint, implementing this training in a home setting is promising; as technology advances, portable VR systems could be developed to allow patients to continue their rehabilitation in a familiar environment. While initial costs for VR setups may be higher than traditional therapies, the potential for improved outcomes and reduced need for extensive clinical therapy could lead to overall long-term cost-effectiveness. Therefore, establishing a home-based NMT training program combined with VR could not only improve accessibility but also empower patients to take charge of their rehabilitation process.

4.2. Limitation

This study is conducted as a pilot investigation, which implies certain constraints on the generalizability and robustness of the findings. The preliminary nature of the study suggests that further research with larger sample sizes is warranted to corroborate and extend the results. Indeed, one notable limitation is the relatively small size of the sample population. The restricted number of participants might limit the statistical power of the analysis and increase the susceptibility to sampling biases. Moreover, at baseline (T0), there exists significant inter-group variability in both error scores and response times during the Stroop test, this significance is not consistently detected in other administered tests. This variability could potentially confound the interpretation of the results, as it may reflect pre-existing differences between groups that are unrelated to the experimental manipulation. Addressing this limitation may require additional statistical controls or subgroup analyses to disentangle the effects of interest from baseline differences. Another limitation may be the use of the Stroop scenario during training for both the experimental and control groups, which raises concerns about potential interference with the results. However, it is essential to clarify that the exercises were specifically designed to engage similar cognitive processes, aiming to improve inhibition skills without directly replicating the Stroop test conditions (in this scenario was included arithmetic exercises and denomination of the number and words with incongruent semantic information). This design supports the interpretation that the observed differences in results are due to the effectiveness of the combined VR and NMT training rather than practice effects. Finally, more investigation on motor outcomes is needed to better understand the relationship between music and immersive VR environment in neurorehabilitation.

5. Conclusions

In conclusion, this pilot study is the first to combine NMT with CAREN technology in patients with PD. Our findings suggest the use of NMT as effective additional method to improve cognitive and EF in PD within an immersive VR environment. Specifically, the EG showed significant improvements in various key cognitive areas compared to the CG. Results related to general cognitive functions and EF assessments demonstrated notable progress, suggesting a positive impact of our combined treatment. Additionally, attention processes, inhibition control and processing speed, evaluated with the Stroop test and Visual Search tasks, showed marked improvements in the EG, highlighting the effectiveness of this approach in enhancing these abilities. In contrast, the CG exhibited significant improvements only in a single parameter of Stroop test (i.e., time). This discrepancy further underscores that the usage of music stimuli through NMT techniques, coupled with the advanced audio-visual feedback provided by VR, appears to be particularly effective in stimulating executive and cognitive functions. These aspects should be taken into account for future studies, since they are crucial for managing deficits associated with Parkinson's disease, offering an innovative and potentially more effective approach compared to traditional treatments.

CRediT authorship contribution statement

Federica Impellizzeri: Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Maria Grazia Maggio:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Paolo De Pasquale:** Validation, Supervision, Software. **Mirjam Bonanno:** Visualization, Validation, Supervision. **Lilla Bonanno:** Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Investigation, Formal analysis, Data curation. **Rosaria De Luca:** Visualization, Validation, Supervision, Methodology, Data curation. **Giuseppe Paladina:** Visualization, Validation, Methodology, Investigation, Data curation. **Angela Alibrandi:** Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **Demetrio Milardi:** Visualization, Validation, Supervision, Conceptualization. **Michael Thaut:** Writing – review & editing, Visualization, Validation, Supervision, Methodology. **Corene Hurt:** Writing – original draft, Visualization, Validation, Supervision. **Angelo Quartarone:** Visualization, Validation, Supervision, Funding acquisition. **Rocco Salvatore Calabrò:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization.

Data Availability Statement

The data supporting this article are not publicly available but can be obtained from the corresponding author upon reasonable request.

Funding Statement

This work was supported by Current Research Funds 2024 from the Ministry of Health, Italy.

Declaration of competing interest

The authors declare no conflicts of interest regarding the research, authorship, or publication of this article.

References

[1] M. Riccò, L. Vezzosi, F. Balzarini, G. Gualerzi, S. Ranzieri, C. Signorelli, et al., Prevalence of Parkinson disease in Italy: a systematic review and meta-analysis, Acta Biomed. 91 (3) (2020) e2020088.
[2] A.H.V. Schapira, K.R. Chaudhuri, P. Jenner, Non-motor features of Parkinson disease, Nat. Rev. Neurosci. [Internet] 18 (7) (2017) 435–450, https://doi.org/10.1038/nrn.2017.62.
[3] R. Baschi, A. Nicoletti, V. Restivo, D. Recca, M. Zappia, R. Monastero, Frequency and correlates of subjective memory complaints in Parkinson's disease with and without mild cognitive impairment: data from the Parkinson's disease cognitive impairment study, J. Alzheimer's Dis. 63 (3) (2018) 1015–1024.
[4] R. Monastero, C.E. Cicero, R. Baschi, M. Davì, A. Luca, V. Restivo, et al., Mild cognitive impairment in Parkinson's disease: the Parkinson's disease cognitive study (PACOS), J. Neurol. 265 (5) (2018) 1050–1058.
[5] P. Barone, A. Antonini, C. Colosimo, R. Marconi, L. Morgante, T.P. Avarello, et al., The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease, Mov. Disord. 24 (11) (2009) 1641–1649.
[6] R. Tang, S. Gong, J. Li, W. Hu, J. Liu, C. Liao, Efficacy of non-pharmacological interventions for sleep quality in Parkinson's disease: a systematic review and network meta-analysis, Front. Neurosci. 21 (2024) 18.
[7] Y. Chen, J. Sun, J. Tao, T. Sun, Treatments and regulatory mechanisms of acoustic stimuli on mood disorders and neurological diseases, Front. Neurosci. 5 (2024) 17.
[8] S.J. Lee, A.L. Dvorak, J.N. Manternach, Therapeutic singing and semi-occluded vocal tract exercises for individuals with Parkinson's disease: a randomized controlled trial of a single session intervention, J. Music Ther. 61 (2) (2024) 132–167.
[9] S. Bhandarkar, B.V. Salvi, P. Shende, Current scenario and potential of music therapy in the management of diseases, Behav. Brain Res. 458 (2024) 114750.
[10] J. Cancela, E.M. Moreno, M.T. Arredondo, P. Bonato. Designing auditory cues for Parkinson's disease gait rehabilitation. In: 2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE; 2014. p. 5852–5.
[11] M. Murgia, R. Pili, F. Corona, F. Sors, T.A. Agostini, P. Bernardis, et al., The use of footstep sounds as rhythmic auditory stimulation for gait rehabilitation in Parkinson's disease: a randomized controlled trial, Front. Neurol. 24 (2018) 9.
[12] S.D. Bella, C.E. Benoit, N. Farrugia, P.E. Keller, H. Obrig, S. Mainka, et al., Gait improvement via rhythmic stimulation in Parkinson's disease is linked to rhythmic skills, Sci. Rep. 7 (1) (2017) 42005.
[13] S.D. Bella, D. Dotov, B. Bardy, V.C. de Cock, Individualization of music-based rhythmic auditory cueing in Parkinson's disease, Ann. N. Y. Acad. Sci. 1423 (1) (2018) 308–317.
[14] R. De Luca, D. Latella, M.G. Maggio, S. Leonardi, C. Sorbera, G. Di Lorenzo, et al., Do patients with PD benefit from music assisted therapy plus treadmill-based gait training? An exploratory study focused on behavioral outcomes, Int. J. Neurosci. 130 (9) (2020) 933–940.
[15] M. Thaut, Rhythm, Music, and the Brain, Routledge, 2013.
[16] G.C. McIntosh, S.H. Brown, R.R. Rice, M.H. Thaut, Rhythmic auditory-motor facilitation of gait patterns in patients with Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 62 (1) (1997) 22–26.
[17] M.H. Thaut, G.C. McIntosh, R.R. Rice, R.A. Miller, J. Rathbun, J.M. Brault, Rhythmic auditory stimulation in gait training for Parkinson's disease patients, Mov. Disord. 11 (2) (1996) 193–200.
[18] M.H. Thaut, V. Hömberg. Handbook of neurologic music therapy. In 2014. Available from: https://api.semanticscholar.org/CorpusID:141514987.
[19] C. Thaut. Training Manual for Neurologic Music Therapy. CO: Colorado State University. Fort Collins; 1999.
[20] K. Mertel, Therapeutical instrumental music performance (TIMP), in: M.H. Thaut, V. Hoemberg (Eds.), Handbook of Neurologic Music Therapy, Oxford University Press, Oxford, 2014, pp. 116–139.
[21] S.D. Bella, C. Benoit, N. Farrugia, M. Schwartze, S.A. Kotz, Effects of musically cued gait training in Parkinson's disease: beyond a motor benefit, Ann. N. Y. Acad. Sci. 1337 (1) (2015) 77–85.
[22] J. Lei, N. Conradi, C. Abel, S. Frisch, A. Brodski-Guerniero, M. Hildner, et al., Cognitive effects of rhythmic auditory stimulation in Parkinson's disease: a P300 study, Brain Res. 1716 (2019) 70–79.
[23] R.S. Calabrò, A. Naro, V. Cimino, A. Buda, G. Paladina, G. Di Lorenzo, et al., Improving motor performance in Parkinson's disease: a preliminary study on the promising use of the computer assisted virtual reality environment (CAREN), Neurol. Sci. 41 (4) (2020) 933–941.

[24] A. Ashoori, D.M. Eagleman, J. Jankovic, effects of auditory rhythm and music on gait disturbances in Parkinson's disease, Front. Neurol. 11 (2015) 6.
[25] M.G. Maggio, R.P. Cezar, D. Milardi, D. Borzelli, C. de Marchis, A. D'Avella, et al., Do patients with neurological disorders benefit from immersive virtual reality? A scoping review on the emerging use of the computer-assisted rehabilitation environment, Eur. J. Phys. Rehabil. Med. 60 (1) (2024).
[26] A. Gangemi, R. De Luca, R.A. Fabio, P. Lauria, C. Rifici, P. Pollicino, et al., Effects of virtual reality cognitive training on neuroplasticity: a quasi-randomized clinical trial in patients with stroke, Biomedicines 11 (12) (2023) 3225.
[27] C. Formica, L. Bonanno, D. Latella, M.C. Ferrera, G. Maresca, A.L. Logiudice, et al., The effect of computer assisted rehabilitation environment (CAREN) in cognitive impairment and coping strategies in Parkinson's disease: a preliminary study, Sci. Rep. 13 (1) (2023) 2214.
[28] R.B. Postuma, D. Berg, M. Stern, W. Poewe, C.W. Olanow, W. Oertel, et al., MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (12) (2015) 1591–1601.
[29] Z.S. Nasreddine, N.A. Phillips, V. Bédirian, S. Charbonneau, V. Whitehead, I. Collin, et al., The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment, J. Am. Geriatr. Soc. 53 (4) (2005) 695–699.
[30] M. Hamilton, A rating scale for depression, Available from, J. Neurol. Neurosurg. Psychiatry [internet]. 23 (1) (1960) 56–62, https://jnnp.bmj.com/content/23/1/56.
[31] B. Dubois, A. Slachevsky, I. Litvan, B. Pillon, The FAB, Neurology 55 (11) (2000) 1621–1626.
[32] C.J. Golden, S.M. Freshwater. Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. 2002. Stoelting; 2002.
[33] S.S. Della, M. Laiacona, H. Spinnler, C. Ubezio, A cancellation test: its reliability in assessing attentional deficits in Alzheimer's disease, Psychol. Med. 22 (4) (1992) 885–901.
[34] E.C. Harrison, G.M. Earhart, The effect of auditory cues on gait variability in people with Parkinson's disease and older adults: a systematic review, Neurodegener. Dis. Manag. 13 (2) (2023) 113–128.
[35] R.G. Brown, C.D. Marsden, Cognitive function in Parkinson's disease: from description to theory, Trends Neurosci. 13 (1) (1990) 21–29.
[36] L.L. Brown, J.S. Schneider, T.I. Lidsky, Sensory and cognitive functions of the basal ganglia, Curr. Opin. Neurobiol. 7 (2) (1997) 157–163.
[37] F.A. Middleton, P.L. Strick, Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies, Brain Cogn. 42 (2) (2000) 183–200.
[38] G. Leisman, R. Melillo, The basal ganglia: motor and cognitive relationships in a clinical neurobehavioral context, Rev. Neurosci. 24 (1) (2013).
[39] S.A. Kotz, A. Stockert, M. Schwartze, Cerebellum, temporal predictability and the updating of a mental model, Philos. Trans. R. Soc., B 369 (1658) (2014) 20130403.
[40] Y.N. Wang, X.N. Wen, Y. Chen, N. Xu, J.H. Zhang, X. Hou, et al., Effects of movement training based on rhythmic auditory stimulation in cognitive impairment: a meta-analysis of randomized controlled clinical trial, Front. Neurosci. 15 (2024) 18.
[41] S.A. Kotz, M. Schwartze, M. Schmidt-Kassow, Non-motor basal ganglia functions: a review and proposal for a model of sensory predictability in auditory language perception, Cortex 45 (8) (2009) 982–990.
[42] M. Schwartze, P.E. Keller, A.D. Patel, S.A. Kotz, The impact of basal ganglia lesions on sensorimotor synchronization, spontaneous motor tempo, and the detection of tempo changes, Behav. Brain Res. 216 (2) (2011) 685–691.
[43] S.A. Kotz, M. Schmidt-Kassow, Basal ganglia contribution to rule expectancy and temporal predictability in speech, Cortex 68 (2015).
[44] G. Schlaug, E. Altenmüller, M. Thaut, Music listening and music making in the treatment of neurological disorders and impairments, Music. Percept. 27 (4) (2010) 249–250.
[45] N. Shimizu, T. Umemura, M. Matsunaga, T. Hirai, Effects of movement music therapy with a percussion instrument on physical and frontal lobe function in older adults with mild cognitive impairment: a randomized controlled trial, Aging Ment. Health 22 (12) (2018) 1614–1626.
[46] P. Pohl, N. Dizdar, E. Hallert, The Ronnie Gardiner Rhythm and Music Method – a feasibility study in Parkinson's disease, Disabil. Rehabil. 35 (26) (2013) 2197–2204.
[47] M. Hars, F.R. Herrmann, G. Gold, R. Rizzoli, A. Trombetti, Effect of music-based multitask training on cognition and mood in older adults, Age Ageing 43 (2) (2014) 196–200.
[48] P. Pohl, E. Wressle, F. Lundin, P. Enthoven, N. Dizdar, Group-based music intervention in Parkinson's disease – findings from a mixed-methods study, Clin. Rehabil. 34 (4) (2020) 533–544.
[49] J.A. Grahn, M. Brett, Rhythm and beat perception in motor areas of the brain, J. Cogn. Neurosci. 19 (5) (2007) 893–906.
[50] M.H. Thaut, G.P. Kenyon, M.L. Schauer, G.C. McIntosh, The connection between rhythmicity and brain function, IEEE Eng. Med. Biol. Mag. 18 (2) (1999) 101–108.
[51] M. Boso, P. Politi, F. Barale, E. Enzo, Neurophysiology and neurobiology of the musical experience, Funct. Neurol. 21 (4) (2006) 187–191.
[52] O. Monchi, M. Petrides, A.P. Strafella, K.J. Worsley, J. Doyon, Functional role of the basal ganglia in the planning and execution of actions, Ann. Neurol. 59 (2) (2006) 257–264.
[53] J. Doyon, H. Benali, Reorganization and plasticity in the adult brain during learning of motor skills, Curr. Opin. Neurobiol. 15 (2) (2005) 161–167.
[54] G. Leisman, A. Moustafa, T. Shafir, Thinking, walking, talking: integratory motor and cognitive brain function, Front. Public Health 25 (2016) 4.
[55] S.C. Herholz, E.B.J. Coffey, C. Pantev, R.J. Zatorre, Dissociation of neural networks for predisposition and for training-related plasticity in auditory-motor learning, Cereb. Cortex 26 (7) (2016) 3125–3134.
[56] D.J. Levitin, A.K. Tirovolas, Current advances in the cognitive neuroscience of music, Ann. N. Y. Acad. Sci. 1156 (1) (2009) 211–231.
[57] J.A. Bugos, W.M. Perlstein, C.S. McCrae, T.S. Brophy, P.H. Bedenbaugh, Individualized Piano Instruction enhances executive functioning and working memory in older adults, Aging Ment. Health 11 (4) (2007) 464–471.
[58] M. Bonanno, P. De Pasquale, C. De Marchis, A. Lombardo Facciale, G. Paladina, B. Fonti, et al., Might patients with cerebellar ataxia benefit from the computer assisted rehabilitation ENvironment (CAREN)? A pilot study focusing on gait and balance, Front. Bioeng. Biotechnol. 24 (2024) 12.
[59] F. Impellizzeri, A. Naro, G. Basile, A. Bramanti, F. Gazia, F. Galletti, et al., Does cybersickness affect virtual reality training using the computer assisted rehabilitation environment (CAREN)? Preliminary results from a case-control study in Parkinson's disease, Physiother. Theory Pract. 38 (13) (2022) 2603–2611.