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Effects of musically cued gait training in Parkinson's disease: beyond a motor benefit

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Auditory stimulation via rhythmic cues can be used successfully in the rehabilitation of motor function in patients with motor disorders. A prototypical example is provided by dysfunctional gait in patients with idiopathic Parkinson's disease (PD). Coupling steps to external rhythmic cues (the beat of music or the sounds of a metronome) leads to long-term motor improvements, such as increased walking speed and greater stride length. These effects are likely to be underpinned by compensatory brain mechanisms involving cerebellar–thalamocortical networks. Because these areas are also involved in perceptual and motor timing, parallel improvement in timing tasks is expected in PD beyond purely motor benefits. In keeping with this idea, we report here recent behavioral data showing beneficial effects of musically cued gait training (MCGT) on gait performance (i.e., increased stride length and speed), perceptual timing (e.g., discriminating stimulus durations), and sensorimotor timing abilities (i.e., in paced tapping tasks) in PD patients. Particular attention is paid to individual differences in timing abilities in PD, thus paving the ground for an individualized MCGT-based therapy.

Keywords: rhythm; Parkinson's disease; movement disorders

Introduction

Gait disorders, common in older adults, are a major challenge for the healthcare system and a growing economic burden for society, given the steady increase in the aging population. Dysfunctional gait (i.e., a slow, broad-based shuffling and cautious walking pattern; "senile gait disorder")[1] is observed in about one-third of the population above 70 years of age among community-residing older adults,[2] a proportion increasing with age.[3] In particular, reduced gait speed, a strong predictor of disability, healthcare utilization, nursing home admission, and mortality,[4,5] is treated as a warning sign anticipating cognitive decline and making it possible to predict its onset.[6] Gait dysfunctions are a major cause of falls in older adults.[7] Among community-dwelling older adults over 64 years of age, approximately 28–35% of people experience falls.[8]

Gait disorders assume dramatic proportions in patients suffering from idiopathic Parkinson's disease (PD).[9] PD is the second most common neurodegenerative disorder (after Alzheimer's disease) and the most serious movement disorder.[10] Typical motor impairments observed in PD, such as slowness of movement, limb rigidity, and postural instability, cause gait disorders, more visible at late stages of the illness.[11] Gait in PD patients is typically characterized by small steps (i.e., reduced stride length), lower cadence associated with reduced gait speed, together with festination and freezing (i.e., difficulty in gait initiation or stopping when turning or approaching an obstacle).[12] Gait disorders limit patients' functional independence, increase the

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likelihood of falls,[9,11,13] and may eventually lead to institutionalization.

Auditory cueing for gait rehabilitation in PD

Cardinal motor symptoms in PD can be alleviated by pharmacological treatment and deep-brain stimulation. However, the beneficial effects of these treatments on gait dysfunctions are typically limited and decrease over time.[9,14,15] Physical therapy represents a valuable alternative for the treatment of gait disorders in PD. This approach is noninvasive, cost efficient, and likely to slow down the progress of the disease.[16] In particular, there is clinical evidence that gait can be improved by asking PD patients to walk along with rhythmic sounds, such as a metronome or music.[17–19]

The patient walking together with rhythmic auditory cues, such as a repeated isochronous sound (i.e., metronome) or music with a salient beat structure,[20–23] typically walks faster, increases step length,[20,24–26] and tends to walk without showing freezing episodes.[27] Notably, beneficial effects of cueing are not confined to gait in the presence of the stimulus. Long-term positive effects on walking in everyday life (i.e., faster gait speed and greater stride length with a reduction of freezing phenomena) even in the absence of stimulation are reported following cueing-based training programs.[18,22] The duration of this carryover effect on noncued gait is still a matter of debate. In some studies an important reduction of the benefits of cueing is observed 4–6 weeks after training,[28] whereas stable cueing benefits are reported in other studies.[29,30]

Explaining the effects of cueing training in PD

In spite of the fact that the clinical benefits of auditory cueing are well known, there is a paucity of research on its neuronal underpinnings. To shed light on the neuronal circuitry underlying this effect of auditory cueing, we rely on a model of temporal prediction and timing developed in the context of auditory processing at different levels of stimulus complexity (language,[31] speech,[32,33] and tones[34]). The framework includes two networks as shown in Figure 1. The basal ganglia–thalamocortical network (BGTC) is engaged in the attention-dependent evaluation of temporal intervals and self-generation of movements. The network is involved in action initiation and explicit timing (i.e., overt estimate of stimulus duration). The cerebellar–thalamocortical network (CTC) is involved in the preattentive encoding of event-based temporal structure and matching of movements to exogenous cues.[33,35] In the healthy brain the BGTC and CTC networks afford the extraction of temporal features of a predictable auditory sequence (e.g., the musical beat), the development of temporal expectations via entrainment, and the coupling of action to salient events in the temporal structure. The functionality of the BGTC network breaks down in PD owing to a progressive loss of neurons in the substantia nigra.[36] The disruption of the BGTC network is responsible for the cardinal motor symptoms of PD. In addition, dopamine depletion, a characteristic of this disorder, leads to malfunctioning of the BGTC network involved in timing mechanisms.[35,37,38] Accordingly, PD patients display timing deficits in a variety of timing tasks.[39–41] Structuring actions in time appears to be a key element for achieving precise and stable coordinated steps during gait. One cause of gait disorders in self-initiated and self-paced movements may thus be an impaired timing system.

One possible explanation of the beneficial effects of auditory cueing may rely on the residual activity of the BGTC network. Such activity may afford a minimal degree of temporal processing of the external stimuli (e.g., beat extraction[42,43]), which may be sufficient to support movement initiation and execution. Another possibility, which has been recently put forward, is that coupling movement to an external auditory stimulus during the training reinforces the CTC network typically spared or affected lately in PD.[44] This network would act as a compensatory mechanism capable of enhancing motor behavior in PD.[45,46] Presenting an external auditory cue to which the patients can synchronize their steps provides a temporal scaffolding needed for pacing steps while walking by regularizing temporal input to the timing system. External temporally predictable cues generate temporal expectations,[47,48] allowing one to predict when the following event (e.g., a step) should occur. These expectations can regularize and stabilize movement by synchronizing the timing of an action execution to the beat structure of an auditory stimulus.[45] There is evidence in favor of the hypothesis of a compensatory mechanism involving the CTC network. Cerebellar connections to the SMA are hyperactivated when action is externally cued.[49] Moreover,

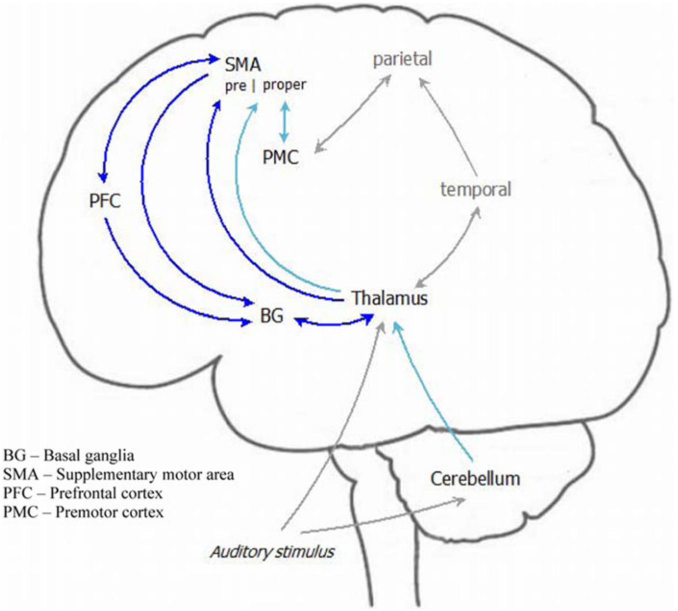

Figure 1. BGTC and CTC networks in Parkinson's disease during auditory cueing. The BGTC circuitry impaired in PD is indicated in blue, whereas cyan highlights the CTC network recruited during auditory cueing. Gray indicates additional circuitry involved by auditory cueing but not part of the compensatory network per se.

activity of the cerebellar anterior lobule is enhanced following 1 month of cueing-based training.[50]

The hypothesis that gait dysfunctions in PD are rooted in timing deficits, and that asking patients to couple steps to auditory cues enhances temporal processing with visible benefits on gait performance, leads to two predictions. First, there is increasing evidence that individuals differ in their abilities to synchronize movement to the beat of an auditory stimulus (e.g., with finger tapping[51,52]). This is also true of patients with PD.[53] Because training with auditory cues is based on the ability of patients to execute steps in correspondence with the stimulus beat, it is expected that those patients, who are the least impaired in synchronizing to the beat, are also those maximally benefiting from the training. Second, the aforementioned circuitry, which is likely to underpin the beneficial effects of auditory cueing, is part of a domain-general system affording both perceptual and motor timing.[35,38,54] Therefore, we anticipate that cueing training may not merely improve motor control during gait but that it additionally enhances perceptual and motor timing beyond gait (e.g., in tasks such as synchronized hand tapping or duration discrimination).

Study 1: effect of musically cued gait training on gait kinematics

In spite of the fact that auditory cueing is widely used for gait rehabilitation, its success is not consistent across studies and varies across individuals.[19] There is a need to better understand the factors leading to such variability in order to devise individualized and efficient gait training in PD. As mentioned above, we hypothesize that sensorimotor timing abilities may account, in part, for this variability and provide a useful means to predict whether a given patient may particularly benefit from the training (i.e., a responder). Patients showing relatively unimpaired sensorimotor synchronization with an auditory cue are expected to maximally benefit from the training. This hypothesis has been tested in a recent study (Benoit *et al.*, unpublished data) in which we examined the role of preintervention sensorimotor timing abilities and individualized cueing frequency as predictors of the effect of a 1-month auditory cueing training program. Fifteen right-handed nondemented patients with PD, showing moderate symptoms of the disease (mean H&Y stage = 2; $SD = 0.7$; mean UPDRS score = 37.7; $SD = 18.8$), were submitted to musically cued gait training

(MCGT). The patients were compared with a control group of 20 right-handed, age-matched nondemented healthy adults.

In the training, which took place at the Clinic of Cognitive Neurology at the University Hospital of Leipzig, Germany, patients walked along with a familiar German folk song without lyrics; the beat of the song was emphasized by a superimposed salient high-pitch bell sound. Cueing frequency (i.e., beat rate of the music) was set to 10% above or below each patient's preferred gait cadence. This individualized frequency was the one leading to the longest stride as assessed in preliminary testing. Each training session lasted 30 minutes. The patients underwent three training sessions per week for 1 month. Medication was kept constant over the whole course of the study. Spatiotemporal gait parameters (i.e., stride length and gait speed) were assessed at the patient's preferred gait cadence before, right after, and 1 month after the MCGT using a Vicon MX motion capture system. In addition, synchronization to auditory stimuli was examined before the training by asking patients to walk to the beat of the same familiar folk song used in the training, presented at a faster (+10%) or slower tempo (−10%) relative to their comfortable gait speed.

The results showed benefits of the MCGT on spatiotemporal gait parameters, which were sustained 1 month after the training. Patients, as compared to controls, showed slower speed (868.5 mm/s vs. 964.4 mm/s for controls; $t(33) = 1.7$, $P < 0.05$) and shorter stride length (980.4 mm vs. 1152.0 mm; $U = 76$, $P < 0.01$). After the training, patients' performance improved significantly in noncued gait. They showed faster gait speed (929.7 mm/s; $W = -66$, $P < 0.05$) and greater stride length (1037.0 mm; $W = -70$, $P < 0.05$). This effect was maintained 1 month after the end of the training (for speed, $W = -82$, $P < 0.01$; for stride length, $W = -78$, $P < 0.05$). The patients' gait speed tested posttraining and at follow-up improved to the level of controls. Notably, there were important individual differences among the patients. Four of them did not respond to training, while the others ($n = 11$; responders) exhibited beneficial effects of MCGT on noncued gait. For responders, stride length increased after the training by 2.1–38.6% relative to the performance before the training. As a result of MCGT, two of them improved their speed to the level of controls.

To test whether the success of MCGT was related to patients' individual performance in synchronization to auditory cues during walking before the training, the percentage of improvement in stride length and speed in noncued gait as a result of the training was correlated to synchronization performance measured before the training. In the scatter graphs presented in Figure 2, the y-axis represents the change of performance with respect to stride length and speed when participants were presented with music with a beat rate that was 10% faster or slower than their preferential gait cadence. In addition, the interstep interval was considered. The x-axis represents the change in stride length owing to the MCGT. As can be seen, the patients best responded to the training if they showed high sensitivity to the fastest cueing frequency (+10%) before the training with respect to stride length and speed and to the slowest frequency (−10%) for stride length only. In addition, higher effectiveness of the training was associated with longer interstep intervals. Similar results were obtained when gait speed was considered the outcome measure.

In sum, these findings confirmed the effectiveness of MCGT in that our 1-month training improved spatiotemporal gait parameters in a group of 15 PD patients under noncued gait conditions. Nevertheless, the response to MCGT varied considerably across patients. One potential cause of such variability lies in differences in sensorimotor synchronization abilities assessed before the training (e.g., coupling steps to a faster or slower beat). We thus found evidence in support of the hypothesis that spared synchronization skills are associated with the improvements owing to MCGT.

Study 2: effect of MCGT on perceptual and motor timing

In this second study[53] we tested whether MCGT leads to beneficial effects beyond gait in perceptual and motor timing. Effects of auditory cueing beyond gait kinematics have not been systematically investigated so far. To test these effects, the same patients and matched controls who participated in the first study were submitted to a battery of timing and sensorimotor tasks before, immediately after, and 1 month after the training. The battery adopted for this purpose is the Battery for the Assessment of Auditory Sensorimotor and Timing

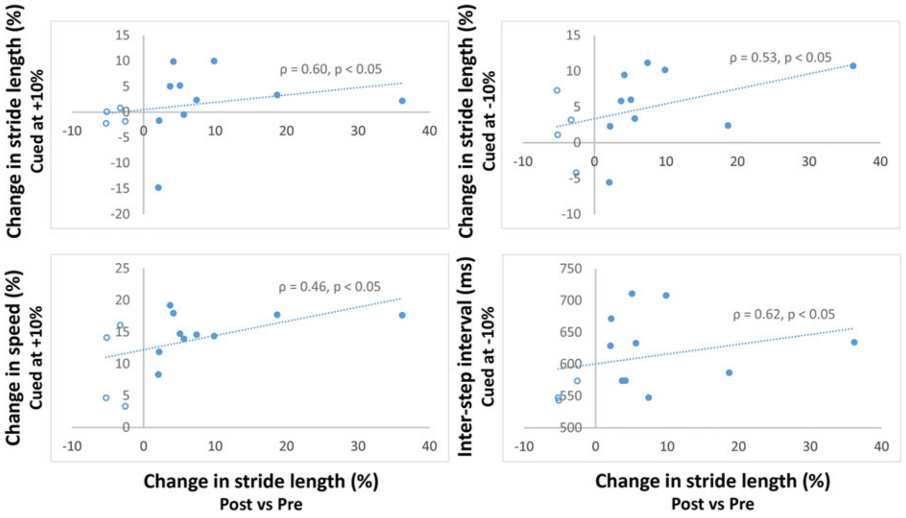

Figure 2. Study 1: Relation between gait improvement owing to the MCGT and the performance in cued gait before the training. Change in stride length (*x* axis) in noncued gait after the training is expressed in percentage relative to pretraining gait performance. Positive values indicate an improvement, negative values a worsening of the performance. Filled circles indicate responders and empty circles nonresponders. From Benoit *et al.* (unpublished data).

Abilities (BAASTA).[53] The BAASTA consists of four perceptual timing tasks and five sensorimotor timing tasks. Perceptual timing tasks include duration discrimination, anisochrony detection with tones,[55] and anisochrony detection with musical stimuli.[51] In these three tasks discrimination and detection thresholds are estimated using a maximum-likelihood adaptive procedure (MLP)[56] implemented in the MLP Matlab toolbox.[57] The fourth perceptual task is the Beat Alignment Task (BAT[58,59]), in which the sensitivity to the alignment of a metronome to the beat of a musical excerpt is assessed. Motor timing tasks involve hand/finger tapping[60–62] in the presence or absence of a rhythmic stimulus. The tasks include nonpaced tapping, synchronized tapping with isochronous sequences and, with music, a synchronization–continuation task,[63–65] and an adaptive tapping task to examine the ability to adapt to tempo changes in a synchronization–continuation task.[66]

The effect of MCGT on perceptual and motor timing was examined selectively for those tasks of the BAASTA wherein patients showed poor performance relative to controls before the training. The average results in these tasks are reported in Figures 3 and 4 for perceptual and motor tasks, respectively. Interestingly, patients showed improvements in perceptual timing that appeared only 1 month following the training in the duration discrimination task ($W = 66.0$, $P < 0.05$) and in the BAT task ($W = -49.0$, $P = 0.07$, marginally significant; interonset interval of musical beat = 600 ms, $W = -37.0$, $P < 0.05$). In spite of the fact that the patients exhibited worse detection of anisochronies in musical stimuli than controls ($U = 87.5$, $P < 0.05$), the training did not improve their performance. As observed for perceptual timing, the MCGT was beneficial for motor timing, an effect that emerged mostly at follow-up evaluation. The training enhanced synchronization accuracy with the isochronous sequences at the slowest tempo (at 750 ms; $W = 72.0$, $P < 0.05$) as observed in the follow-up session; only a trend toward improved accuracy immediately after the training was observed for isochronous sequences at the fastest tempo (450 ms, $W = 50$, $P = 0.08$). No other improvement was observed in motor timing. Training was effective only in improving the detection of tempo changes, as a part of the adaptive tapping task, an effect visible at follow-up ($W = -43$, $P < 0.05$).

To sum up, the patients tested in this study exhibited impaired perceptual timing across all BAASTA tasks except for the anisochrony detection in isochronous sequences. Nevertheless, motor timing was relatively spared before the training with the exception of decreased accuracy in tapping

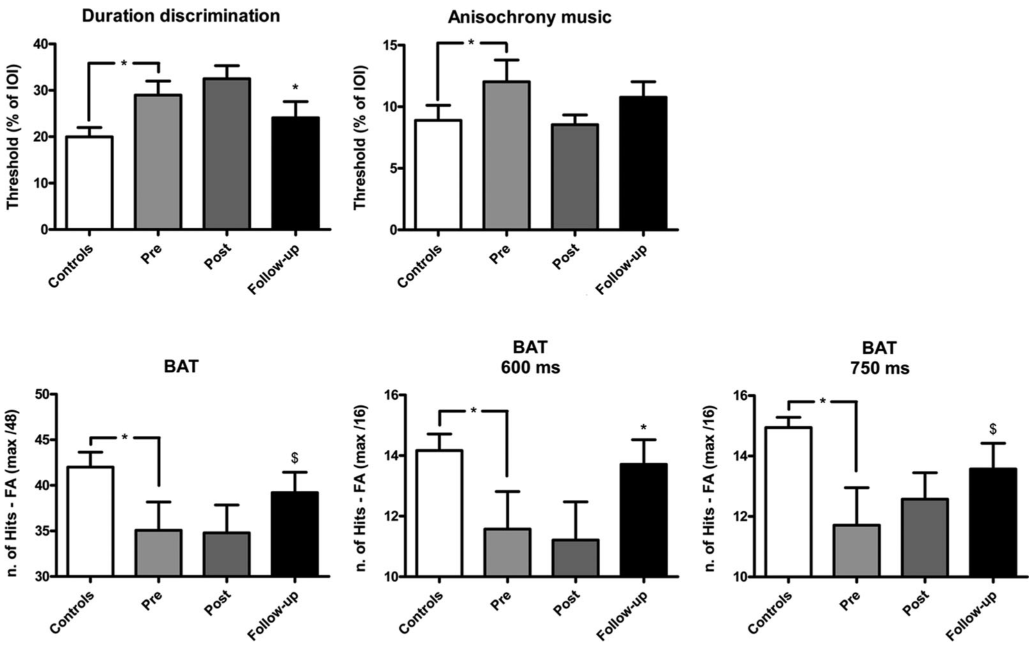

Figure 3. Study 2: Performance of PD patients and controls in the perceptual tasks of the BAASTA. Error bars indicate the standard error of the mean (SEM). Note: $^{*}P < 0.05$; \$ = marginally significant difference. From Benoit *et al.*[53]

along with an isochronous sequence. These findings generally confirm previous evidence that PD is associated with timing disorders.[39,41,67–71] Thorough testing of perceptual and motor timing abilities before and after the training revealed a stable effect of training on timing tasks beyond gait performance

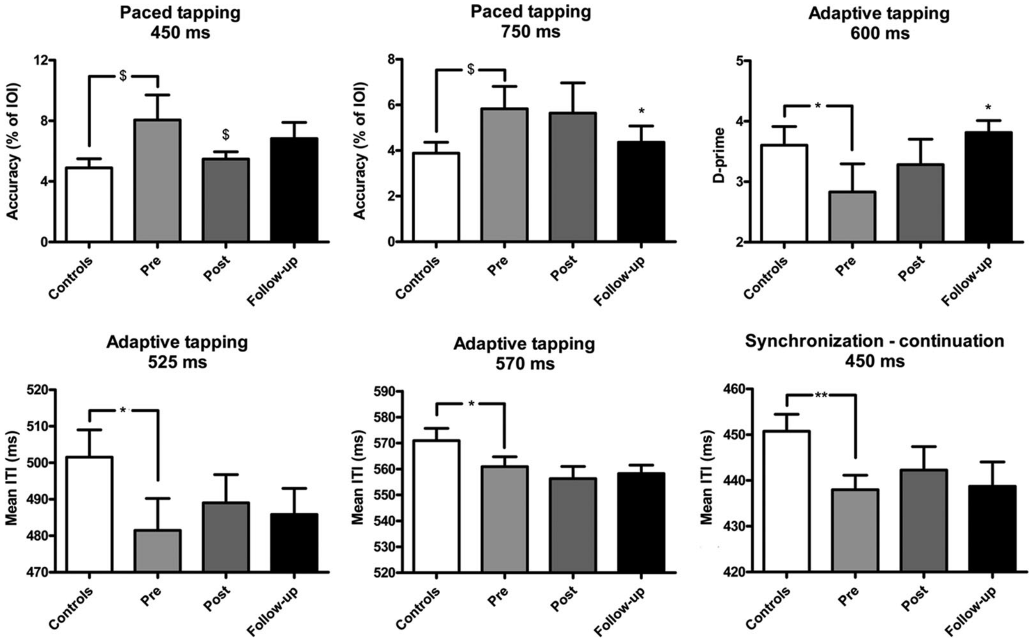

Figure 4. Study 2: Performance of PD patients and controls in the motor tasks of the BAASTA. Error bars indicate the standard error of the mean (SEM). Note: $^{*}P < 0.05$; $^{**}P < 0.01$; \$ = marginally significant difference. From Benoit *et al.*[53]

even after the training ended. In most of the cases this effect was manifest 1 month after the training. The mechanisms leading to such a delayed effect of MCGT are still unclear. One possibility is that additional practice (e.g., walking with music at home after the end of the training program) may have further improved perceptual and sensorimotor timing. This explanation cannot be fully excluded in spite of the fact that the patients were not encouraged to do so and that the cueing device was not made available to the patients after the training. Another possibility is that because the BAASTA was administered three times, learning may have affected perceptual and motor timing abilities. Although learning is unlikely to fully account for the effects of training, because of the observed individual differences (i.e., delayed effects of training in some patients versus immediate effects of training in others), carryover effects associated with the repetition of the same tasks should be considered in further studies.

Conclusions

The two studies summarized here are consistent with the hypothesis that gait disorders in PD are rooted in timing deficits. By asking patients to synchronize steps to rhythmic sound cues using auditory cueing training such as MCGT, gait spatiotemporal parameters can be improved with benefits, which are sustained in the absence of stimulation. Sensorimotor timing is a crucial skill needed for synchronizing steps to an auditory cue. This ability is critical for predicting the success of training programs based on auditory cueing in gait rehabilitation. This fact has important consequences for the optimization of existing training strategies based on auditory cueing, by developing an individualized approach to rehabilitation, tailored to the patient's spared abilities and needs. Moreover, this finding suggests that some patients with gait disorders who reveal poor synchronization abilities and poor response to an auditory cue should be immediately directed toward alternative strategies (e.g., body-weighted treadmill training). Finally, the observation that benefits of auditory cueing training extend beyond gait, more generally to perceptual and motor timing, is relevant for theories about the functional and neuronal underpinnings of timing in performance and perception. These findings have important clinical implications, suggesting that auditory cueing training may be effective for remediating nonmotor deficits in PD (e.g., language-related deficits).[72] Interestingly, this may represent a step toward the development of novel strategies for training cognitive aspects of PD, extending beyond motor symptoms. Training targeted to cognitive functioning may be highly needed because PD affects not only movement but also cognition.[73] Training schemes bridging motor performance coupled to an external auditory stimulus and cognition may pave the way for the development of novel rehabilitation strategies to reduce cognitive decline in PD.

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Conflicts of interest

The authors declare no conflicts of interest.

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