Parkinsonism and Related Disorders 96 (2022) 57–64

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

What about the role of the cerebellum in music-associated functional recovery? A secondary EEG analysis of a randomized clinical trial in patients with Parkinson disease

Antonino Naro [a], Loris Pignolo [b], Daniele Bruschetta [c], Rocco Salvatore Calabrò [a,*]

[a] IRCCS Centro Neurolesi Bonino Pulejo, Messina, Italy
[b] Istituto di Riabilitazione S.Anna, Crotone, Italy
[c] Azienda Ospedaliera Universitaria Policlinico G.Martino, Messina, Italy

ARTICLE INFO

Keywords:
Gait rehabilitation
Parkinson's disease
Rhythmic auditory stimulation
Cerebellum

ABSTRACT

Rhythmic Auditory Stimulation (RAS) has been shown to be of help in an effective gait training of people with idiopathic Parkinson's disease (PD). The cerebellum may play an important role in RAS aftereffects by compensating the detrimental internal clock for automatic and rhythmic motricity. However, the neurophysiological mechanisms underlying RAS aftereffects are still poorly understood. In the present study, we tested the contribution of the cerebellum to RAS-based gait training aftereffects in people with PD by examining cerebellum-cerebral connectivity indices using standard EEG recording. We enrolled 50 patients with PD who were randomly assigned to two different modalities of treadmill gait training using GaitTrainer3 with and without RAS (non_RAS) during an 8-week training program. We measured clinical and kinematic gait indices and electrophysiological data (standard EEG recording during walking on GaitTrainer3) of both the gait trainings. We found that the greater improvement in gait performance following RAS than non_RAS training, as per clinical and kinematic assessment, was paralleled by a more evident reshape of cerebellum-brain functional connectivity with regard to specific brain areas (pre-motor, sensorimotor and temporal cortices) and gait-cycle phases (mainly 25–75% of the gait cycle duration). These findings suggest that the cerebellum mediates the reshape of sensorimotor rhythms and fronto-centroparietal connectivity in relation to specific gait-cycle phases. This may be consistent with a recovery of the internal timing mechanisms generating and controlling motor rhythmicity, eventually improving gait performance. The precise definition of the cerebellar role to gait functional recovery in people with PD may be crucial to create patient-tailored rehabilitative approaches.

1. Introduction

The irregularity of walking pace is one of the main feature of gait impairment in Parkinson's disease (PD), beyond reduced stride length and step velocity, increased cadence, and freezing of gait. This pattern depicts a disturbance of coordinately rhythmic locomotion [1]. In particular, patients with PD complain of a difficulty in performing automatized movements, including walking, owing to the dopaminergic output failure among basal ganglia and other brain areas, including the supplementary motor area, the inferior-parietal cortex and the cerebellum [1,2]. This latter oversees predictable movement sequencing by exerting an inhibitory action [2].

The use of acoustic stimuli within neurologic music therapy has been employed, among others, to retrain locomotor coordination to improve gait in PD [3–5]. Actually, it has been demonstrated that Rhythmic Auditory Stimulation (RAS), a technique of Neurologic Music Therapy, enhances the connection between rhythmical auditory perception and motor behavior, thus complementing pharmacological therapy in PD to improve overall gait performance [5,6].

The physiological mechanisms underpinning music therapy are partially known. Indeed, it has been proposed that RAS may produce a compensation of specific cerebello-thalamo-cortical networks involved in internally-paced rhythmic movement regulation [7]. Specifically, auditory rhythm (i.e., the repetitive structure of sounds across time) synchronizes motor network functions via motor entrainment between auditory and motor cortices [5]. This also involves brain areas in

* Corresponding author. IRCCS Centro Neurolesi Bonino Pulejo, via Palermo, SS113, C.da Casazza, 98124, Messina, Italy.
E-mail address: salbro77@tiscali.it (R.S. Calabrò).

https://doi.org/10.1016/j.parkreldis.2022.02.012
Received 5 January 2021; Received in revised form 6 February 2022; Accepted 17 February 2022
Available online 23 February 2022

audio-motor networks, including the cortico-striatal, the cortico-cerebellar, and the premotor-primary sensorimotor ones [8]. Indeed, RAS might act on the cortico-striatal system through direct projections from auditory cortical regions to the striatum, which should foster the inhibition of unwanted movements, the selection of desired movements, the internal rhythmic events sequencing, and beat's sensorimotor implementation in motor plans, thus providing an input for sequential movements and automatized processes [8,9].

In addition, RAS may act on the cortical systems through a network among auditory, premotor, supplementary motor, and primary motor cortical regions. Indeed, RAS has been shown to activate motor areas even during resting state, in analogy to what reported during movement observation [10]. Indeed, visual and/or auditory stimulation pertinently coupled to motor execution may foster the reactivation of formerly acquired motor patterns [10,11]. Therefore, coupling motor training to beats may be useful to retrain motor coordination, even beyond the stimulation period, in analogy to what occurs during motor training coupled to visuomotor feedback [12]. In this vein, RAS may compensate for an impaired internal timing mechanism by providing an external timing signal [3–6,12].

Lastly, an important contribution of the cerebellum to RAS-mediated effects has been proposed. Cerebellar output may compensate for the detrimental cortico-striatal functioning by processing the auditory inputs concerning online tuning of motor coordination at fast tempos [9,13,14]. This processing occurs through a subcortical-thalamo-cortical loop encompassing the cerebellum, the basal ganglia, SMA, and pre-SMA, which may be involved in temporal prediction of beats (i.e., movements) [9,13,14]. In this vein, the cerebellum may contribute to rhythmic auditory-motor synchronization [9,13,14]. Particularly, the cerebellum may sustain the temporal processing by hyper-activating the premotor areas during action sequencing, as a compensatory effect for dopaminergic depletion. The strategic importance of cerebellum-premotor network probably lies in the fact that premotor areas may contain specific audiovisual mirror neurons that have been postulated to play a key role when gait and music are paired [15]. In this complex scenario, the cerebellum is proposed to attempt vicariating basal ganglia failure concerning, among other, motor rhythmicity.

RAS-based rehabilitation thus aims to strengthen these alternative pathways to trigger compensatory mechanisms for sequential movement impairment. It has been hypothesized that pairing step with RAS may render predictable step sequencing, thus retraining the internal mechanisms of motor sequencing and, eventually, improving gait performance [12]. In this regard, RAS may entrain a wide cortical network among premotor, sensorimotor, and temporo-occipital areas, which seems to bypass or facilitate the impaired cortico-striatal functioning [3–6,12–15].

In the present study, we tested the contribution of the cerebellum to the effects of RAS-based gait training in PD by examining cerebellum-cerebral EEG connectivity, seeking whether RAS influences such a connectivity through the three above mentioned neural systems controlling motor performance. Detecting a detrimental cerebellar output may indeed help identifying the patients whose motor program must include cerebellar functions in order to improve gait.

2. Materials and methods

2.1. Participants and study design

This study is part of a previous clinical trial (https://clinicaltrials.gov/ct2/show/NCT03434496) investigating the role of treadmill plus RAS in improving gait and balance in idiopathic PD individuals [12]. Briefly, 50 patients were randomized in two groups; the experimental group (EG; n = 25) underwent an intensive treadmill gait training with RAS using the GaitTrainer3 (GT3) (Biodex, Shirley, NY, US), whereas the control group (CG; n = 25) was provided with an equally intensive treadmill gait training without RAS. More details are provided in Table 1 and the supplemental material file.

2.2. Intervention

See the supplemental material file.

2.3. Outcomes

Patients were assessed before (TPRE) and after (TPOST) the rehabilitation training using the Functional Gait Assessment (FGA), the Unified Parkinson's Disease Rating Scale (UPDRS), the Berg Balance Scale (BBS), the Tinetti Falls Efficacy Scale (FES), the 10-m walking test (10MWT), the timed up-and-go test (TUG), and the gait quality index (GQI) derived from gait analysis. Furthermore, they underwent EEG recording while walking on the treadmill once the fully adapted to the rehab training (i.e., when the target gait of 108bpm was reached; on average, the third-fourth session) and the last day of training, usually 5–10min after the session started. Specifically, we sought the cerebellum's temporal dynamics by assessing EEG sources resulting from gait, presupposing such task-related cerebellar activity as spatially and temporally distinct from the source activity measured in sensorimotor cortices.

2.4. EEG recording and analysis

See the supplemental material file.

2.5. Statistical analysis

See the supplemental material file.

3. Results

3.1. Baseline

There were no significant clinical-demographic differences between the two groups (Table 1). Additionally, there were no significant differences in gait and balance tasks and in overground gait performance (as per GQI) between the groups (all $p > 0.1$). Indeed, both groups showed a weak GQI.

Concerning EEG data, we assessed the spatial distribution of the significant activities (z-scores) in the cortex and the cerebellum within the four relevant sample time-points during gait (0–25%, 25–50%,

Table 1
Summary of the clinical-demographic characteristics measured with subjects in ON anti-Parkinsonian medications.Data are reported as mean ± standard deviation.

group	age(y)	gender F/M	dd(y)	H&Y	MMSE	comorbidities risk factors		LEED (mg/day)
EG (n = 25)	70 ± 8	9/11	10 ± 3	3 ± 1	26 ± 3	None diabetes mellitus hypertension dyslipidemia tabagism alcoholism	4 4 7 4 5 1	450 ± 55
CG (n = 25)	73 ± 8	6/14	9.3 ± 3	3 ± 1	25 ± 3	None diabetes mellitus hypertension dyslipidemia tabagism alcoholism	5 4 6 3 6 1	435 ± 49
p-value	0.7	0.4	0.3	0.1	0.2	0.7		0.7

Legend: CG control group(non-RAS treadmill gait training); dd disease duration; EG experimental group(RAS treadmill gait training); F female; H&Y Hoehn and Yahr score; LEDD levodopa equivalent daily dosage; M male; MMSE: Mini Mental Status Examination; UPDRS: Unified Parkinson's Disease Rating Scale.

50–75%, and 75–100% of the gait-cycle) (Fig. 1). These time points were relative to stride cueing in the EG and to simple gait-phases in the CG. In both groups, we found a significant gait-related activation (whether $p < 0.0002$) in the left central and parietal areas (corresponding to BA4-paracentral lobule and BA1) during the 0–25% of the gait-cycle and during the swing-phase of left-limb (i.e., contralateral to the right-HS). Such activation involved both central and parietal areas during the 25–75% of the gait-cycle (i.e., during left-limb swing completion and initiation or right-limb swing up to the midswing). Finally, it was restricted to the right central and parietal areas (i.e., contralateral to the left-HS) during the 75–100% of the gait-cycle (i.e., the left-swing completion) (Fig. 1). A high activation of both the frontal areas (likely including BA6 -PMC and SMA, BA9 -DLPFC, and BA10 -anterior-PFC) was also appreciable during the entire gait-cycle (Fig. 2). Lastly, a significant bilateral cerebellar activity (likely corresponding to the lobule VI-Crus I) was observed during the 25–75% of the gait-cycle (Fig. 2).

3.2. Clinical and gait outcome

All patients completed the scheduled training without reporting any side effects, and none of the patients withdrew from any treatment session.

Both trainings yielded a significant improvement in FES, FGA, and UPDRS, but the changes were of greater magnitude in the EG than in the CG. Conversely, the groups equally improved in BBS and TUG. The 10MWT non-significantly improved in both groups (Fig. 3).

Gait features improved significantly in both groups but more evidently in the EG than in the CG. This occurred for GQI, stance/swing ratio, step-cadence, stride-length (Fig. 4). Contrariwise, gait-cycle duration decreased equally in both groups whereas gait speed increased equally (Fig. 4).

3.3. EEG data

Following GT3 training, we observed a partial reduction of the frontal area activation observed at baseline along the entire gait-cycle ($p < 0.0001$) (Fig. 1), with particular regard to the 0–25% of the gait-cycle, but with a slight increase in the 25–75% of the gait-cycle (Figs. 1–2). Moreover, we found a potentiation of the centroparietal areas activation ($p < 0.0001$) in the 25–75% of the gait-cycle. In

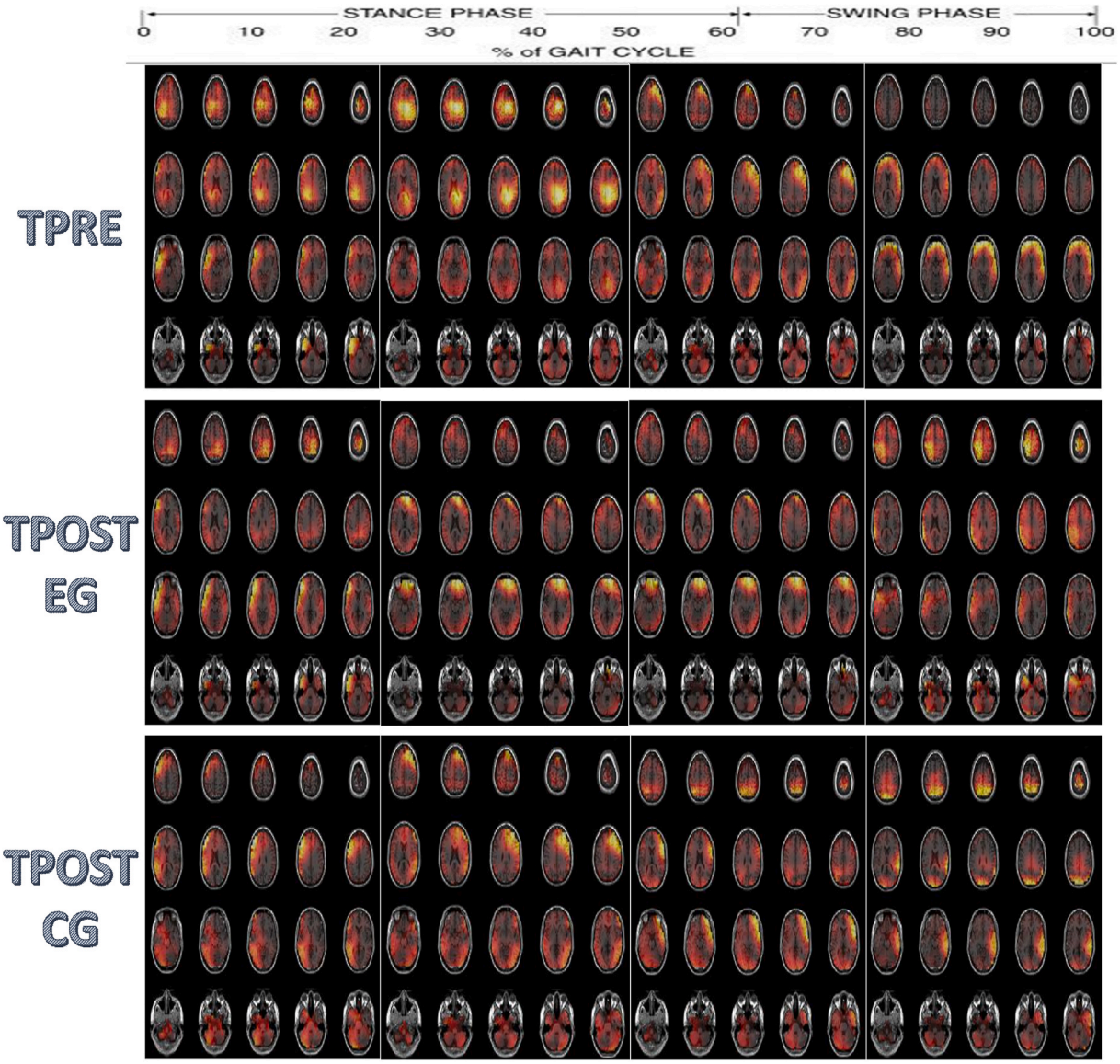

Fig. 1. Group-average source maps of spatiotemporal patterns of activity with z-score values at each of the gait cycle phases (0–25, 25–50, 50–75, and 75–100%), group (EG and CG), and assessment (TPRE and TPOST).

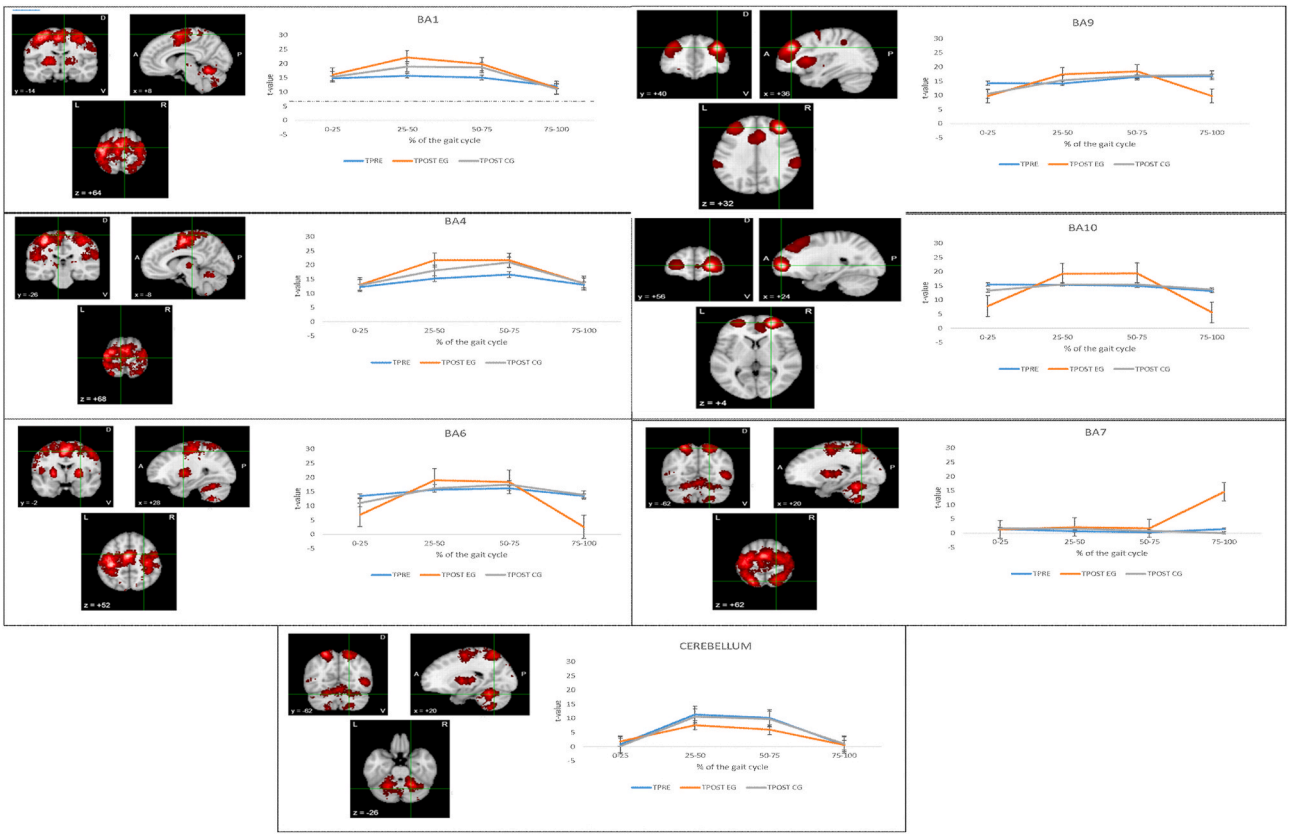

Fig. 2. The time course of the local maxima of the regions showing functional activation (t-value, thresholded at corrected $p < 0.0002$ –dotted line) at each of the gait cycle phases (0–25, 25–50, 50–75, and 75–100%), group (EG and CG), and assessment (TPRE and TPOST). Activity is shown for the maximum amplitude vertex within each ROI during the gait epoch.

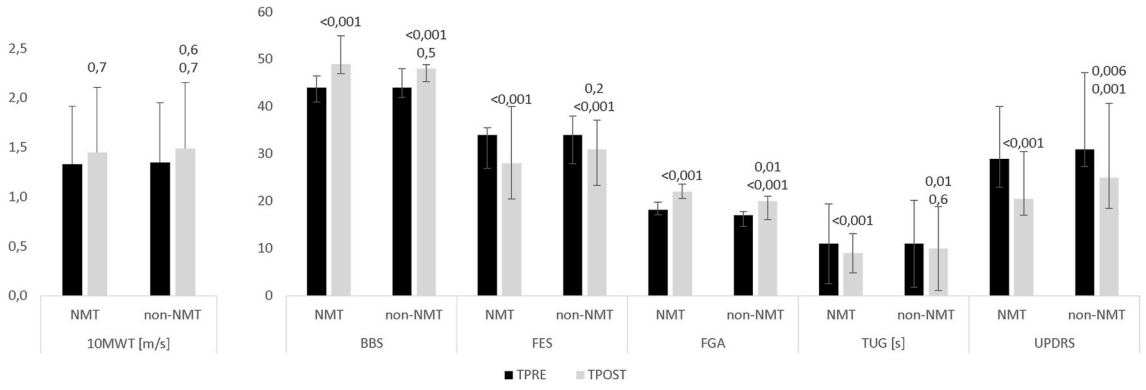

Fig. 3. Effects of gait training on clinical parameters from the baseline (TPRE) to the end of the rehabilitation period (TPOST). Data are reported as mean/median and standard deviation/interquartile range (vertical error bars). Superscript numbers represent the p-values of within-group and between-group (#) changes.

addition, an activation of the parieto-occipital areas in the 75–100% of the gait-cycle was appreciable instead of the frontal areas ($p = 0.0001$) (Figs. 1–2). Lastly, there was a reduction of cerebellar activity in the 25–50% (approximately on the more lateral portions) (Fig. 1; $p < 0.0001$) and in the 50–75%of the gait-cycle (approximately on the posterior cerebellum) (Fig. 2; $p < 0.0001$).

In the CG, the reduction of frontal activation was significant ($p = 0.003$) but even slighter as compared to the EG (between-group difference $p = 0.001$) (Figs. 1–2)A potentiation of the centroparietal areas activation was appreciable ($p = 0.002$), but it was milder than that observed in the EG (between-group difference $p < 0.001$). Furthermore, it lacked the gait-cycle specificity observed in the EG (Figs. 1–2). Finally, the cerebellar activation observed at baseline was substantially non-modulated after the end of the conventional treadmill gait training ($p = 0.3$) as compared to the EG (between-group difference $p < 0.0001$) (Figs. 1–2).

Noteworthy, the phase-synchronization analysis using the imaginary part of coherency for detecting gait-induced functional connectivity between O1/O2 and the whole EEG sensor activity showed non-significant within-group ($p = 0.7$) and between-group ($p = 0.9$) values. Finally, the interpolation analysis showed that there were significant differences (all $p < 0.001$) in both the neighboring and distant pair-electrodes (Supplemental Fig. 1).

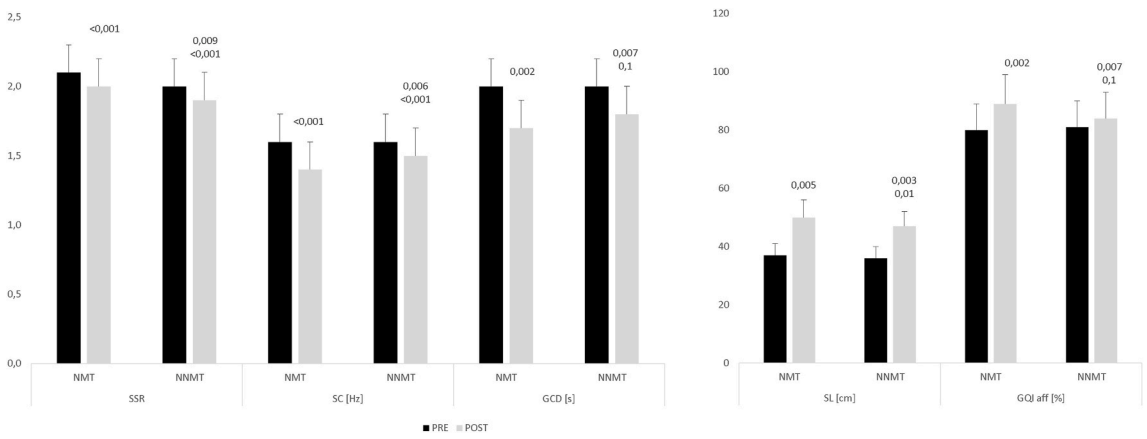

Fig. 4. Effects of gait training on gait kinematic parameters from the baseline (TPRE) to the end of the rehabilitation period (TPOST). Data are reported as mean/median and standard deviation/interquartile range (vertical error bars). Superscript numbers represent the p-values of within-group and between-group (#) changes.

3.4. Clinical-electrophysiological correlations

We considered the FGA and the GQI as the main outcome measures to be tested for clinical-electrophysiological correlations, as they reflect the overall improvement in gait performance after gait training [13]. Indeed, the improvement of the combined outcome significantly correlated with the decrease in activity within the frontal ($r = 0.699, p = 0.00003$) and cerebellar regions ($r = 0.810$, $p < 0.00001$)and with the increase in activity within the central ($r = 0.519, p = 0.004$) and parietal regions ($r = 0.695, p = 0.00004$) (Fig. 5).

4. Discussion

In our previous work, we hypothesized that the improvement in gait performance in PD patients following RAS-based gait training may depend on the activation of specific cerebello-thalamo-cortical motor networks that could compensate for the detrimental BG-thalamo-cortical motor network functions related to the internal timing processing, like the one occurring in cued gait or rhythmic movements [8–12,16–18]. Indeed, the present data suggest that some gait-related cerebellar source activities are temporally and spatially consistent with cued gait in PD patients. Particularly, an increased interaction between auditory and executive networks, paralleled by a high activation of the cerebellum (likely the lobules VI and Crus I) and the sensorimotor areas during the mid-phase of the gait cycle and a hypoactivation of frontal areas, particularly at the beginning of the gait cycle, were appreciable. We may therefore hypothesize that PD patients suffer from a deficit of motor programming and gait initiation, as suggested by the frontal hypoactivity, which seems to be compensated by a strong cerebellar output to the sensorimotor cortices (that may be entrained by the temporal rhythmic auditory information) [8] in the attempt to compensate the frontal detrimental output. This hypothesis is consistent with the adaptive role of the cerebellum concerning gait performance maintenance. In fact, the lateral regions of the cerebellum seemed more active during gait. These are known to be functionally interconnected with frontoparietal regions that sustain some executive functions, including working memory, planning, organizing, and strategy formation, which are all critical for motor programming and (re) learning [19–21]. Furthermore, the EEG findings were significantly different between RAS-based gait training and conventional treadmill gait training, even though our approach has a low spatial resolution, given that such cerebellar activations were demonstrated using a standard EEG recording (for the first time ever, to the best of our knowledge). Notwithstanding, our data may suggest the contributing role of

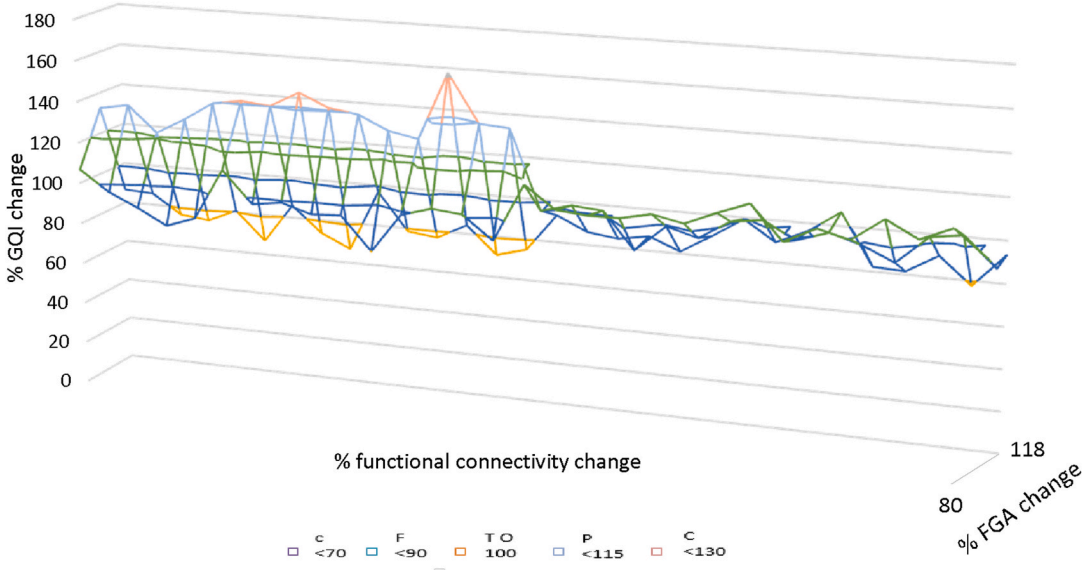

Fig. 5. Scatterplot graphs for the correlation between the clinical (FGA and GQI) and neurophysiological data (% functional connectivity change) within cerebellar (c), frontal(F), temporo-occipital (TO), parietal(P), and central(C) areas.

the cerebellum concerning RAS-based motor performance and in improving gait and balance in response to RAS-based gait training in patients with PD [16–18].

Despite the compensating role of the cerebellum during cued gait is promising, an over-activation of the cerebellum may although worsen gait as suggested by studies of non-invasive cerebellar stimulation in PD [22]. As an alternative hypothesis, we may thus propose that PD patients may primarily suffer from a detrimental cerebellum output to frontal regions, which may in turn account for the detrimental fronto-centro-parietal output and, consequently, the sensorimotor hyperactivation.

One could concern that both hypotheses do not contemplate primarily the changes in excitability of the primary motor cortex. However, such activation is more evident in relation to task complexity rather than to gait adaptation.

Beyond the primary or secondary role of the cerebellum in motor adaptation tasks, the emerging data is the functional impairment of the cerebellum concerning motor adaptation and gait control in PD patients, which is recovered by an intensive, cued gait training. Particularly, the deterioration of basal ganglia-cerebellum circuitry may account for a reduced LTD of Purkinje cells in locomotor training, which may account for sensorimotor high activation [25]. In fact, the inhibitory tone that the cerebellum normally exerts over the primary motor cortex is reduced in cerebellar patients after a treadmill training with motor adaptation [25]. Furthermore, when the cerebellum ant the motor cortex co-activate, there is a shift from LTD to LTP mechanisms of motor adaptation and learning [25]. This was not the case of patient provided with conventional treadmill gait training, as they still showed a cerebellar high activity after the training. Additionally, it has been proposed that STN pathological activity, characterized by burst activity and higher firing rates, may in turn be responsible for the hyperactivity of cerebellar cortex leading to alterations in the cerebello-thalamo-cortical circuits [23]. In this regard, it has been shown that rhythmic cerebellar stimulation by means of oscillatory transcranial currents delivered at frequencies resembling an intrinsic musical tempo largely shapes fronto-parietal connectivity and the sensorimotor rhythms related to the fine regulation of gait parameters [24]. Therefore, it is likely that the cerebellum can still contribute to the internal timing mechanisms when properly stimulated by rhythmic external cues, or at least acoustic cues, thus further suggesting a (mal)adaptive functional activity of the cerebellum in PD.

Therefore, our data suggest that the cerebellum actively contributes to compensate the internal clock deficit within the basal ganglia system, which is a basic function of the feedforward control exerted by the cerebellum on movement [9,13,20–23]. The improvement in gait cycle features and performance related to precise timing of muscle activity significantly correlated with cerebellar activity modulation, thus suggesting a restoration of either the timing mechanisms or the internal-clock model within the cerebellum and the basal ganglia [9,13,20–23]. The underlying mechanism may consist in a compensatory cortico-subcortical networks such as cerebello–thalamo–cortical circuitries or by the residual activity of cortico-striatal networks [8,9,13,20–23]. This intimal correlation between the cerebellum and the basal ganglia is consistent with the recent findings on the two- and tri-synaptic pathways linking the cerebellum and basal ganglia, suggesting thus a possible computational role of the cerebellum [8,9,13,20–23]. In this regard, a direct causal modeling analysis revealed differential modulation of effective connectivity strength between the basal ganglia and the cerebellum in performing a timed motor task [8,9,13,20–23]. Even though the activity in cerebellum we found may be consistent with fMRI studies, we have to acknowledge that the differences in temporal and spatial resolution preclude a direct mapping between time course of gait-related EEG and fMRI activity. Lastly, increased level of dopamine were found in the basal ganglia after cerebellar activation, suggesting that gait training aimed at stimulating cerebellar functions may be useful to restore dopaminergic tone, which is known to have a central role in the internal clock functionality within the basal ganglia.

Beyond the putative pathophysiological meaning of our findings, our data suggest that the cerebellum plays an important role in determining the clinical effects of RAS-based gait training. Actually, patients provided with RAS-based gait training showed a significant gait performance improvement, as suggested by the steeper step, the more stable gait, and the reduced stepping frequency with greater stride length. Both the reduction of cerebellar activation and the increase in frontal activation significantly correlated with gait performance improvement. Conversely, conventional treadmill gait training only partially increased frontal activation and did not significantly affect cerebellar activation.

The clear discrepancy between the aftereffects of the trainings may depend on the specific entrainment of the audiovisual mirror neuron system, which is active when an action is heard, seen, or performed (as in the case of RAS-based gait training) [15]. Previous works illustrated that the activation of frontal (including ventral and dorsal premotor cortex) and posterior brain regions (particularly the visuomotor association areas) seems to be related to the activation of the motor system when an individual is provided with purely perceptual event dissociated from action processes [15]. In particular, movement synchronization with auditory rhythms engage motor regions of the brain, even in the absence of overt movement, including the PMC, SMA, pre-SMA, and the lateral cerebellum, thus suggesting a tight auditory-motor coupling when sounds are meaningful to the motor system [3–6,16–18]. In this scenario, the cerebellum may integrate sensorimotor information to generate internal models for predictive motor control [19–22]. It should be verified whether these neural responses are specific only to action-related sounds that have a learned auditory-motor mapping [26]. This association allows motor preparation or rehearsal, which are fundamental issue to regain motor function and improve motor performance, consistently with the neuroplasticity-inspired principles of motor (re)learning.

It is true that the auditory rhythm provision (i.e., the repetitive structure of sounds across time) is a main cause of motor network synchronization occurring via motor entrainment (i.e., a temporal locking process in which one system's motion or signal frequency induces another system to take on a related frequency), as properly in the case of RAS-assisted gait training [5,6]. Furthermore, functional connectivity exists between auditory and motor areas at all levels of the motor hierarchy [5,6]. Nevertheless, the simple provision of auditory stimuli may not be sufficient to account for the wide synchronization processes we observed, with particular regard to the specific temporal dynamics of brain activation with respect to the gait cycle phases. However, this should be tested with specific control experiments.

4.1. Study limitations and strengths

EEG recording of the cerebellum is itself rather challenging, given that the arrangement of Purkinje cells in the cerebellar cortex is in a "closed field" configuration [27,28]. The spontaneous EEG cerebellar activity, although potentially appreciable [29,30], is likely too weak to be clearly and robustly detected. However, this can be overcome by increasing the cerebellum activity, e.g., during motor tasks (like in our study) or non-invasive brain stimulation, and adopting non-phase-locked analyses using time-frequency techniques in source space. Nonetheless, it remains challenging to detect high-frequency oscillations, unless using MEG [31].

Sensor coverage undoubtedly represents a limitation of our study. Actually, one may be concerned about the small EEG-channel number we used to record cortical and cerebellar signals, as well as that we did not have available EEG electrode placement over the cerebellum. Therefore, one may argue that it has not been provided sufficient spatial sampling over the regions where cerebellar signals may project. One could solve this limitation using low-tech solutions, such as thoughtful placement of the subject's head under the sensor arrays (at the expense of frontal coverage) [32], or the use of additional free electrodes.

However, Todd et al.showed the power spectrum at cerebellar locations relative to other locations [33],i.e., the cerebellar EEG had a distinct power spectrum compared to the other sensor locations [34,35], which was achievable even using a few electrodes, including PO7,O1, Oz,O2, PO8,PO9,O9,Iz,O10,PO10,CB1,CBz,CB2,SP1, and SP2. Notably, O1/2 and CB1/2 have largely overlapping spectral signals, indicating that the signal at the cerebellar electrodes cannot be explained by a simple summation of activity at neighboring occipital and splenius electrodes. Thus, evidence suggests that a relatively unique signal can be recorded at cerebellar regions [33]. One could criticize that, to date, higher-density electrode headsets are available. However, they carry with some non-negligible issues inherent to costs, setup, interpretation time, number of modulations to be recorded, availability of specific or sufficient procedural billing codes, comfort; furthermore, they are subjected to greater movement artifacts when used during specific situations, including gait training (like in our study) [36].

Another important problem when dealing with cerebellar EEG analysis is the source localization process, in which the traditional spherical head model fitting to the cerebral cortex poorly fits with the cerebellar cortex. To this end, we referred to the most recent works implementing LORETA concerning source localization [37]. The EEG signal arises essentially from a spatial and temporal summation of the underlying electrical activity – both synaptic and spiking. It is then thought that the more intricate folding of the cerebellum would result in the signal from one fold potentially canceling out the signal from the neighboring fold, if signals are of opposite orientation based on the fold position. Moreover, a possible rationale on how the EEG signal is detectable is the laminar organization of pyramidal neurons in the cortex where all dendritic trees are directionally aligned. This leads more readily to coherent summation of activity on the surface. However, unlike pyramidal neurons, the dominant Purkinje neurons in the cerebellum have immense treelike dendritic arborizations. Then, in addition to the folding, this dendritic structure in the cerebellum could also result in opposing orientations at different points and therefore signal cancelation. Source localization studies, which rely on this assumption of the manner of signal summation in the construction of the EEG signal, could therefore not be able to reliably identify cerebellar sources of the signal.

Notwithstanding, even though much can be explored at the sensor level, some authors reported solid data mainly by using a beamformer approach for a source-level analysis [37]. These studies highlighted two main findings. First, a distinct power spectrum is generally reproducible by multiple groups at specific electrode positions. In fact, an ANOVA on cerebellar electrodes power compared with the mean power from the neighboring electrodes showed that the observed power in the cerebellar electrodes during a passive visuomotor task was not simply due to the summation of diffuse signals generated in neighboring regions, in accordance with the observed change in power following the task [33]. Although an interpolation analysis was not performed in this study, the data were consistent with ours coming from the phase-synchronization and the interpolation analysis we carried out (to rule out any connectivity between O1/O2 and other EEG sensor activity), showing that the signal at the O1/O2 electrodes could not be explained by a summation of the activity at neighboring electrodes and that relatively unique signals could be recorded at those electrodes.

Second, power spectrum at cerebellar electrodes is modulated by changes in behavior, and specific single-channel features of the signal (including entropy and complexity measures) can be related to any external behaviors/tasks. This is consistent with the distinct EEG feature changes we found following gait training with and without RAS, supporting the idea that our findings are solidly related to the cerebellum activity. In fact, gait-relevant cerebellar activity was consistently identified across trials. Cerebellar activity always began around 25% of the gait cycle, consistently with prior reports for the onset of motor-related cerebellar activity [33,38]. Cerebellar activation showed a spatial pattern of activity across movement conditions and group averages. Moreover, cerebellar activations were distinct from other cortical ones, including evoked visual activity, supporting that cerebellar activity was not a mislocalized source activity from the cortex.

Both these issues are in support of the reliability of the cerebellar activities we described, despite the simple methodology we adopted and the fact that the feasibility of measuring cerebellar activity using EEG has been already validated [38].

Another limitation of our study is the lack of a follow-up period. However, patients with PD provided with RAS-assisted gait training usually retain the clinical improvement up to three months, and future investigations are needed to verify this issue.

A possible biasing role of conventional physiotherapy beyond the treadmill training deserves further investigation with different control groups. Our aftereffects at both cortical and cerebellar level need to be verified in PD populations different for clinical picture and disease duration, as both these issues can affect patients' clinical and electrophysiological responsiveness to RAS-assisted gait training.

The biasing effects of drug therapy has to be carefully assessed, as our patients were tested in ON state, to gain most from motor practice. However, it has been shown that the effects of RAS do not significantly depend on dopaminergic medication [39].

Finally, a possible role of the patient's appreciation of the music and the individual predisposition to be entrained by music rhythms (i.e., musicality) remains to be investigated.

5. Conclusions

We suggest that the cerebellum may have a compensatory and adaptive role concerning gait function recovery by favoring the precise timing of motor actions along the gait cycle phases. This probably occurs by compensating the deficient internal timing clock within the basal ganglia. However, further studies are required to provide a full understanding of the temporal dynamics of human cerebellum function. Furthermore, our data confirms the feasibility of source localization with regard to gait related cerebellar activations using a standard EEG system and conventional source imaging techniques. Once confirmed, these promising data may serve as a platform to improve the understanding of spatiotemporal activity of the cerebellum with cortex so as to improve the management of gait disorders, including PD. Actually, this knowledge may serve to the patient-tailoring of the gait rehabilitative paradigm by selecting people who may likely benefit from RAS-based gait training and to more objectively monitor patients' progress along the rehab training.

Funding

No funding to be reported.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Institutional Review Board of IRCCS Centro Neurolesi Bonino Pulejo (Messina, Italy) approved the study.

Informed consent

Persons provided their written informed consent to study participation and data publication.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2022.02.012.

References

[1] M.W. Creaby, M.H. Cole, Gait characteristics and falls in Parkinson's disease: a systematic review and meta-analysis, Park. Relat. Disord. 57 (2018) 1–8.
[2] D.S. Peterson, F.B. Horak, Neural control of walking in people with parkinsonism, Physiology 31 (2) (2016) 95–107.
[3] P.A. Rocha, G.M. Porfírio, H.B. Ferraz, V.F. Trevisani, Effects of external cues on gait parameters of Parkinson's disease patients: a systematic review, Clin. Neurol. Neurosurg. 124 (2014) 127–134.
[4] S. Zhang, D. Liu, D. Ye, H. Li, F. Chen, Can music-based movement therapy improve motor dysfunction in patients with Parkinson's disease? Systematic review and meta-analysis, Neurol. Sci. 38 (9) (2017) 1629–1636.
[5] M.H. Thaut, M. Abiru, Rhythmic auditory stimulation in rehabilitation of movement disorders: a review of current research, Music Perception 27 (4) (2010), 263–26.
[6] A. Raglio, Music therapy interventions in Parkinson's disease: the state-of-the-art, Front. Neurol. 6 (2015) 185.
[7] L. Avanzino, E. Pelosin, C.M. Vicario, G. Lagravinese, G. Abbruzzese, D. Martino, Time processing and motor control in movement disorders, Front. Hum. Neurosci. 10 (2016) 63.
[8] K. Braunlich, C.A. Seger, K.G. Jentink, I. Buard, B.M. Kluger, M.H. Thaut, Rhythmic auditory cues shape neural network recruitment in Parkinson's disease during repetitive motor behavior, Eur. J. Neurosci. 49 (6) (2019) 849–858.
[9] S. Nozaradan, M. Schwartze, C. Obermeier, S.A. Kotz, Specific contributions of basal ganglia and cerebellum to the neural tracking of rhythm, Cortex 95 (2017) 156–168.
[10] J.A. Grahn, The role of the basal ganglia in beat perception: neuroimaging and neuropsychological investigations, Ann. N. Y. Acad. Sci. 1169 (2009) 35–45.
[11] O. Löfberg, P. Julkunen, E. Kallioniemi, A. Pääkkönen, J. Karhu, Modulation of motor cortical excitability with auditory stimulation, J. Neurophysiol. 120 (3) (2018) 920–925.
[12] R.S. Calabrò, A. Naro, S. Filoni, M. Pullia, L. Billeri, P. Tomasello, S. Portaro, G. Di Lorenzo, C. Tomaino, P. Bramanti, Walking to your right music: a randomized controlled trial on the novel use of treadmill plus music in Parkinson's disease, J. NeuroEng. Rehabil. 16 (1) (2019) 68.
[13] K. Martinu, O. Monchi, Cortico-basal ganglia and cortico-cerebellar circuits in Parkinson's disease: pathophysiology or compensation? Behav. Neurosci. 127 (2013) 222–236.
[14] A.C. Bostan, R.P. Dum, P.L. Strick, Cerebellar networks with the cerebral cortex and basal ganglia, Trends Cognit. Sci. 17 (2013) 241–254.
[15] S.A. Kotz, M. Schwartze, Differential input of the supplementary motor area to a dedicated temporal processing network: functional and clinical implications, Front. Integr. Neurosci. 5 (2011) 86.
[16] A. Ashoori, D.M. Eagleman, J. Jankovic, Effects of auditory rhythm and music on gait disturbances in Parkinson's disease, Front. Neurol. 6 (2015) 234.
[17] Y. Koshimori, M.H. Thaut, Future perspectives on neural mechanisms underlying rhythm and music based neurorehabilitation in Parkinson's disease, Ageing Res. Rev. 47 (2018) 133–139.
[18] N. García-Casares, J.E. Martín-Colom, J.A. García-Arnés, Music therapy in Parkinson's disease, J. Am. Med. Dir. Assoc. 19 (12) (2018) 1054–1062.
[19] M.F. Vinueza Veloz, K. Zhou, L.W.J. Bosman, et al., Cerebellar control of gait and interlimb coordination, Brain Struct. Funct. 220 (2015) 3513–3536.
[20] M. Manto, J.M. Bower, A.B. Conforto, et al., Consensus paper: roles of the cerebellum in motor control–the diversity of ideas on cerebellar involvement in movement, Cerebellum 11 (2012) 457–487.
[21] C.J. Stoodley, E.M. Valera, J.D. Schmahmann, Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study, Neuroimage 59 (2012) 1560–1570.
[22] J.L. Mirdamadi, Cerebellar role in Parkinson's disease, J. Neurophysiol. 116 (3) (2016) 917–919.
[23] A.C. Bostan, P.L. Strick, The basal ganglia and the cerebellum: nodes in an integrated network, Nat. Rev. Neurosci. 19 (2018) 338–350.
[24] A. Naro, D. Milardi, A. Cacciola, M. Russo, F. Sciarrone, G. La Rosa, A. Bramanti, P. Bramanti, R.S. Calabrò, What do we know about the influence of the cerebellum on walking ability? Promising findings from transcranial alternating current stimulation, Cerebellum 16 (4) (2017) 859–867.
[25] A.R. Gallimore, T. Kim, K. Tanaka-Yamamoto, E. De Schutter, Switching on depression and potentiation in the cerebellum, Cell Rep. 22 (3) (2018) 722–733.
[26] J.L. Chen, V.B. Penhune, R.J. Zatorre, Listening to musical rhythms recruits motor regions of the brain, Cerebr. Cortex 18 (12) (2008) 2844–2854.
[27] S. Ramón y Cajal, La Textura del Sistema Nerviosa del Hombre y los Vertebrados, Moya, Madrid, 1904.
[28] H. Bantli, Multi-electrode analysis of field potentials in the turtle cerebellum: an electrophysiological method for monitoring continous spatial parameters, Brain Res. 44 (1972), 676–645.
[29] E. D'Angelo, C.I. De Zeeuw, Timing and plasticity in the cerebellum: focus on the granular layer, Trends Neurosci. 32 (2009) 30–40.
[30] S.S. Dalal, D. Osipova, O. Bertrand, K. Jerbi, Oscillatory activity of the human cerebellum: the intracranial electrocerebellogram revisited, Neurosci. Biobehav. Rev. 37 (2013) 585–593.
[31] S.D. Muthukumaraswamy, K.D. Singh, Visual gamma oscillations: the effects of stimulus type, visual field coverage and stimulus motion on MEG and EEG recordings, Neuroimage 69 (2013) 223–230.
[32] I. Hashimoto, T. Kimura, M. Tanosaki, Y. Iguchi, K. Sekihara, Muscle afferent inputs from the hand activate human cerebellum sequentially through parallel and climbing fiber systems, Clin. Neurophysiol. 114 (2003) 2107–2117.
[33] N. Todd, S. Govender, J.G. Colebatch, The human electrocerebellogram(ECeG) recorded non-invasively using scalp electrodes, Neurosci. Lett. 682 (2018) 124–131.
[34] J. Retif, Study of the spontaneous electric activity of the human cerebellum, Acta Neurol. Psychiatr. Belg. 64 (1964) 825–831.
[35] E. Niedermeyer, The electrocerebellogram, Clin. EEG Neurosci. 35 (2004) 112–115.
[36] S.M. Stoyell, J. Wilmskoetter, M.A. Dobrota, D.M. Chinappen, L. Bonilha, M. Mintz, B.H. Brinkmann, S.T. Herman, J.M. Peters, S. Vulliemoz, M. Seeck, M. S. Hämäläinen, C.J. Chu, High-density EEG in current clinical practice and opportunities for the future, J. Clin. Neurophysiol. 38 (2021) 112–123.
[37] L.M. Andersen, K. Jerbi, S.S. Dalal, Can EEG and MEG detect signals from the human cerebellum? Neuroimage 215 (2020) 116817.
[38] C.I. De Zeeuw, F.E. Hoebeek, L.W. Bosman, M. Schonewille, L. Witter, S. K. Koekkoek, Spatiotemporal firing patterns in the cerebellum, Nat. Rev. Neurosci. 12 (6) (2011) 327–344.
[39] 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. Psychiatr. 62 (1997) 22–26.