UHASSELT

KNOWLEDGE IN ACTION

Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Exploring auditory-motor coupling during finger-tapping and walking to music and metronomes in persons with cerebellar impairments: a pilot case-control study

Anne Bogaert

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
Prof. dr. Peter FEYS

COPROMOTOR :
dr. Lousin MOUMDJIAN

COPROMOTOR :
Prof. dr. Mario MANTO

2021
2022

UHASSELT
KNOWLEDGE IN ACTION

www.uhasselt.be
Universiteit Hasselt
Campus Hasselt:
Martelarenlaan 42 | 3500 Hasselt
Campus Diepenbeek:
Agoralaan Gebouw D | 3590 Diepenbeek

UHASSELT

KNOWLEDGE IN ACTION

Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Exploring auditory-motor coupling during finger-tapping and walking to music and metronomes in persons with cerebellar impairments: a pilot case-control study

Anne Bogaert

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
Prof. dr. Peter FEYS

COPROMOTOR :
dr. Lousin MOUMDJIAN

COPROMOTOR :
Prof. dr. Mario MANTO

Acknowledgements

I would like to express my gratitude to my co-promotor Dr. Lousin Moumdjian for guiding me through the process of establishing this master thesis. Further, I want to thank co-promotor Prof. dr. Mario Manto for providing me insights on the cerebellar population through his expertise in the field. Lastly, I thank my Promotor Prof. dr. Peter Feys and co-promotor Dr. Lousin Moumdjian for bringing this thesis to a higher level through the sharp feedback they provided me with.

I acknowledge the C.H.U. of Charleroi and the University of Hasselt for taking part in this study.

Wijgmaal, 01/06/2022 *A.B*

Research context

The research of co-promotor Dr. Lousin Moumdjian emphasizes on the effects of rhythm-based interventions on motor and cognitive functions in persons with multiple sclerosis and persons with cerebellar impairments. Cerebellar impairments have challenged the neurological rehabilitation science since their ethiology, clinical presentation and underlying mechanisms of action are complex and heterogenous. This thesis project conducted in second master year of 'rehabilitation sciences and physiotherapy' was part of an ongoing observational case-control experimental study at C.H.U. of Charleroi on persons with cerebellar impairments. The official title is: "Understanding the effect of variances on precision in predictive coding when walking to music and metronomes in persons with Cerebellar lesions" and the ClinicalTrials.gov Identifier is: NCT04887753. This study investigates the sensory-motor synchronization abilities of persons with cerebellar impairments during walking to music and metronomes and its effects on gait.

This was a single-master thesis of Anne Bogaert under the supervision of Prof. Dr. Peter Feys, as promotor and Dr. Lousin Moumdjian and Prof. Dr. Mario Manto (C.H.U. of Charleroi) as co-promotors. The thesis was conducted according to a central format. The research questions were determined by the student in cooperation with the co-promotor Dr. Lousin Moumdjian. There was no contribution to the development of the research design and methodology as this was an ongoing study. The data was used from an existing dataset not collected by the student due to collection during periods of internship and limited testing opportunities because of Covid-19. To learn data collection, the student participated in other experimental sessions in a clinical trial similar to the one reported here, under the supervision of Dr. Lousin Moumdjian. The student partly contributed to the data preprocessing and fully contributed to the data analysis and the academic writing process of this master thesis.

Article

TABLE OF CONTENTS

1 ABSTRACT

Background: Persons with cerebellar impairments (PwCI) present with upper limb and gait ataxia due to coordination problems. Task-oriented interventions are needed to improve the mobility of PwCI. The benefit of coupling gait to rhythmic auditory stimuli has been shown in other neurological diseases such as Parkinson's disease and Multiple sclerosis. As the cerebellum contributes to the timing of movement, the applicability of intervention strategies using rhythmic auditory stimuli in PwCI is uncertain and still to be investigated.

Objectives: To invest the ability of PwCI to synchronize their movement to rhythmic auditory stimuli at various tempi with a finger-tapping and a walking paradigm.

Methodology: Five PwCI and five healthy controls (HC's) participated to two experiments: finger-tapping and walking to metronomes and music. Participants were instructed to synchronize their finger-tap or step to the tics of metronomes and the beats in music during one (for tapping) and three (for walking) minutes at various tempi [-12%, -8% -4%, 0%, +4%, +8%, + 12%]. The tempi were calculated from their preferred tapping or walking pace.

Measurements: Synchronisation measures (Resultant vector length, Relative phase angle and Inter-beat deviation) were taken for both experiments and spatiotemporal gait parameters (including gait variability measures) were taken for the walking experiment.

Results: Age, gender, height and weight were similar between PwCI and HC's. Heterogenous clinical presentations and ethiologies (including cerebellar stroke and hereditary cerebellar degenerations) were present in PwCI. Both PwCI and HC's were able to synchronize their finger-tapping to the rhythmic auditory stimuli. In the walking experiment, HC's were able to synchronize but 3 out of 5 PwCI were not. The latter was influenced by the tempi, with -4% showing best synchronisation abilities in PwCI, as well as the lowest step time variability.

Conclusion: Preliminary results indicate that the synchronisation abilities of PwCI are higher when finger-tapping than when walking to rhythmic auditory stimuli. Different mechanisms of action may be present between these tasks. Further investigation in a bigger sample is needed to understand the auditory-motor coupling during walking in PwCI.

Keywords: Auditory-motor coupling, synchronisation, music, metronome, gait, cerebellar impairments

2 INTRODUCTION

"The cerebellum plays an integral role in the control of limb and ocular movements, balance, and walking (Marsden, 2018c, p. 261)". Morton and Bastian (2004) describes that "some of the most distinctive clinical signs of cerebellar damage are impairments of balance and gait." The gait pattern of persons with cerebellar impairments (PwCI), referred to as 'gait ataxia' is characterized by highly variable gait parameters, a significantly reduced step frequency and a prolonged double limb support duration (Stolze et al., 2002). The clinical presentation depends on the ethiology and varies "according to the cerebellar lesion location and extracerebellar signs (Marsden, 2018a)". This heterogeneity of clinical presentation in cerebellar diseases (Pilotto& Saxena, 2018) have made investigation challenging. A commonly used term in the context of cerebellar diseases is 'cerebellar ataxia'. In Marsden (2018) this term was described as: "a movement disorder that can affect balance and gait, limb movement, oculomotor control, as well as cognition and affect. These symptoms significantly impact on functional ability and quality of life (Zhang et al., 2017)". Therefore, it is an important topic for rehabilitation science.

Recent work of Cabaraux, Gandini, and Manto (2021) distinguishes three 'cerebellar syndromes' based on years of expertise with neuroimaging data linked to the clinical presentation of PwCI. The vestibulo-cerebellar syndrome (VCS) is characterized by vertigo, dizziness and oculomotor deficits due to lesions in the posterior cerebellum and it's connections to the oculomotor and vestibular nuclei. The cerebellar motor syndrome (CMS) reflects the typical features of ataxic gait, deficits in postural control, dysmetria and dysarthria due to lesions in the anterior lobules of the cerebellum (lobe I-VI) and secondary in the lobule VIII. The cerebellar cognitive affective syndrome/Schmahmann's syndrome (CCAS/SS) results in dysfunctions of executive functions (planning, abstract reasoning, verbal fluency, working memory), spatial cognition, attentional control and affect. Although the prevalence within the cerebellar population is not clear yet, these cerebellar syndromes could have an important influence on treatment results in this research field.

Marsden (2018b) states that “deficits in balance and walking reflect the cerebellum’s proposed role in coordination, sensory integration, coordinate transformation, motor learning, and adaptation”. The complexity of the cerebellum as a neurological entity demands for novel rehabilitation strategies who challenge these functions. There is moderate evidence that physical therapy may improve postural disorders (Marquer, Barbieri, & Pérennou, 2014), ataxia and daily life functions (Fonteyn et al., 2014) and balance and coordination (He, Zhang, Tang, & Gao, 2021), in persons with degenerative cerebellar diseases. Most of the research on PwCI has been conducted on impairment-based rehabilitation strategies (e.g.; balance- and coordination exercises and conventional physical therapy), while a lesser amount of activity- level rehabilitation (e.g.; gait training, occupational therapy, and virtual Reality-based training) has been investigated (Matsugi, 2017); (Marquer et al., 2014); (He et al., 2021).

Yet another approach is task-oriented training, which has been defined by Winstein & Wolf in chapter 17 of Richard L. Harvey (2008) as: 1) active involvement of the patient while performing a real-life task; 2) progressive and optimally adapted to the patient and; 3) sufficiently challenging (Richard L. Harvey, 2008). As “one of the most characteristic and sensitive signs of cerebellar damage is gait ataxia” (Ilg& Timmann, 2013), task-oriented rehabilitation for the improvement of walking is a highly relevant. A possible way to do this is by using auditory-motor coupling intervention strategies, where the steps are coupled to an external rhythm during walking (Moumdjian, Buhmann, Willems, Feys, & Leman, 2018).

In patients with parkinson’s disease (PD), rhythmic auditory cueing interventions have shown their positive effects on gait and mobility. Authors of this umbrella review suggest that “it should be incorporated into a regular rehabilitation program for patients affected by PD” (Forte, Tocci, & De Vito, 2021). For patients showing freezing of gait, Willems et al. (2006) recommended to use lower tempi (-10%) of a patient’s preferred walking cadence to achieve stride length enlargement. For non-freezers higher tempi (+10%) were recommended to increase gait speed. In persons with multiple sclerosis (PwMS), walking to metronomes and music has been investigated by Moumdjian et al. (2019). Participants were able to synchronize with music and metronomes and walked at higher tempi than their preferred walking cadence with music (up to +8%) and metronomes (up to +10%).

Fundamental research from Nozaradan, Schwartze, Obermeier, and Kotz (2017) showed that the cerebellum specifically contributes to the neural tracking of rhythm. In 11 patients with focal cerebellar lesions, an electroencephalography (EEG) was taken "while they listened to rhythmic sequences known to induce selective neural tracking at a frequency corresponding to the most-often perceived pulse-like beat". The cerebellar patients showed a reduced neural tracking of the beat compared to controls, especially at higher frequencies. Suggesting the perceptual component of auditory-motor coupling may be affected in PwCI, this could hinder the benefits of a task-oriented gait rehabilitation with rhythmic auditory stimuli. Further, a better finger tapping task performance was associated with smaller volumes in the right lobule VI in healthy persons (Baer et al., 2015). Considering this, the lesion location in PwCI may have its influence on the ability to synchronize with auditory stimuli as well.

Therefore, this study aims to invest the ability of persons with cerebellar impairments (PwCI) to synchronize their movement to rhythmic auditory stimuli (tics in metronomes and beats in music) at various tempi with a finger tapping and a walking paradigm. In addition, the effect of the coupling on spatiotemporal gait parameters during the walking paradigm is investigated. The following research questions were formulated:

Primary research questions:

- Can PwCI synchronize their finger tapping to rhythmic auditory stimuli at various tempi? Is the synchronization ability influenced by the type of stimuli (tics in metronomes or beats in music) or the tempo [-12%, -8% -4%, 0%, +4%, +8%, + 12%]?
- Can PwCI synchronize their steps to rhythmic auditory stimuli during walking at various tempi? Is the synchronization ability influenced by the type of stimuli (tics in metronomes or beats in music) or the tempo [-12%, -8% -4%, 0%, +4%, +8%, + 12%]?

Secondary research questions:

- What is the implication of instructed auditory-motor coupling on gait parameters during walking to rhythmic auditory stimuli (tics in metronomes or beats in music) at different tempi [-12%, -8% -4%, 0%, +4%, +8%, + 12%]?

We hypothesize that auditory-motor coupling is possible at lower tempi, as this was not investigated in the study of Nozaradan et al. (2017). To support this further, one case with multiple sclerosis and cerebellar ataxia had the highest synchronization at tempo -12% during a finger-tapping and a walking task in a recent study of (Moumdjian et al., 2022). As an increased variability of step length, stride length, and stride time is highly reported in PwCI (Buckley, Mazzà, & McNeill, 2018) we aim to investigate the potential of walking to rhythmic auditory stimuli at various tempi in order to promote a more natural gait pattern for PwCI.

3 METHODOLOGY

3.1 STUDY DESIGN

This study is a pilot study of an ongoing case-controlled observational study on PwCI and healthy controls (HC). Preliminary data will provide the first insights on the participants and their response to this experiment.

3.2 PARTICIPANTS

3.2.1 Inclusion and exclusion criteria:

Inclusion criteria for PwCI: Persons with a clinically confirmed cerebellar impairment. Ethiologies may diverge from different types of spinocerebellar ataxia's (SCA), MS with cerebellar lesions, paraneoplastic lesions, cerebellar stroke, hereditary degenerative cerebellar diseases amongst others.

Inclusion criteria for HC: Healthy individuals without major diseases or impairments hindering their mobility or independent functioning in daily life.

Exclusion criteria for PwCI and HC: Not able to walk for 12 minutes (walking aids are permitted), deafness, amusia for rhythm and cognitively impaired hindering understanding of the instructions.

3.2.2 Medical ethics

An application was submitted to the ethical committee of Hasselt University and the Marie Curie hospital in CHU Charleroi with as contact person Prof. dr. Mario Manto, head of the department of neurology. This study was approved by the Uhasselt on the 15th of May 2021 with the code B1152021000003 (see appendix for approval document).

3.2.3 Recruitment

Persons with a cerebellar impairment were recruited from the hospital C.H.U. Charleroi and healthy controls were recruited through an announcement at Hasselt University. Each participant signed an informed consent before enrollment in the study.

3.3 EXPERIMENTAL PROCEDURE

The experimental procedure was conducted in three sessions of two hours each, which were one week apart from each other.

In the first session, all demographic data and descriptive test were collected. Demographic data included age, gender, height, weight, education level, work and musical experience. Further, the diagnosis, the date of diagnosis, the clinical presentation and the prescribed treatment were collected. The descriptive test consisted of multiple motor tests, a cognitive-affective test, a beat perception test for detecting amusia and questionnaires, which are specified below in the section *'3.4.1. Descriptive tests and measures'.* The acquisition of a descriptive MRI of each PwCI was performed by the hospital itself on a separate time point.

In the second session, the participants conducted an experimental finger-tapping procedure. They were asked to tap with the index finger of their preferred hand on a custom made sensor pad (Rosso, Leman, & Moumdjian, 2021) with following instructions:

- "First, tap in silence at your preferred rhythm for one minute"
- "Then, try to synchronize your finger tap rhythm with the rhythm provided by the auditory stimuli for one minute"

The stimuli consisted of metronomes and music, which were each provided at 7 different tempi [-12%, -8% -4%, 0%, +4%, +8%, + 12%]. The tempi were calculated from their preferred rhythm measured in the condition in silence. Similarly to the study of Moumdjian et al. (2019) the music was personalized by using a database of songs ranging from 80 to 130 beats per minute, divided in 6 different genres: disco, instrumental, pop, softpop, poprock, and variety (Buhmann& Masson, 2016). Participant could choose the genre for each music condition.

Within the two blocks of music and metronomes (each consisting of 7 conditions) the order of performance was randomized by a computer to avoid a systematic carry-over effect. Between each condition the participant had one minute of rest.

In the third session, the participants conducted a similar experiment, but now while walking. They were equipped with device called a D-jogger (Moens et al., 2014), which provides the auditory stimuli and calculates the synchronization measures. APDM sensors (APDM

wearable technologies Inc, Portland, OR, USA) were used for measuring gait parameters (see below in section *'3.3.1 Equipment'*).

Participants were first asked to walk in silence for three minutes, in order to determine their preferred walking cadence (PWC) and their baseline gait parameters. Subsequently, they were instructed to walk for three minutes and synchronize their steps to tics in metronomes and beats in music provided at 7 different tempi [-12%, -8% -4%, 0%, +4%, +8%, + 12%]. The tempi were calculated from their PWC.

The two blocks (metronomes and music) of 7 conditions (7 tempi) were once again randomized, and the participants received now three minute of rest time between each condition. Fifteen seconds before each condition, the participant started walking in order to be at comfortable gait speed when the auditory stimuli began. Participants using a walking stick in daily life were asked to use a rollator in order to synchronize their step to and not the walking stick the auditory stimuli.

3.3.1 Equipment

For the tapping experiment, a pad containing piezo sensors which was recorded with a Teensy 3.2 microcontroller was used. Participants were provided with the auditory stimuli via DenderfieldShield air-tube earplugs. Synchronization measures were calculated from the timestamps between the finger-taps and the beat onset of the auditory stimuli. This set up was used in previous research on entrainment and auditory-motor coupling (Rosso et al., 2021). In Figure 1, a visualization of the tapping pad is presented.

Figure 1: Costum made sensor pad (Rosso et al., 2021)

For the walking experiment, synchronization was measured by an interactive music player called the D-jogger and it's software (Moens et al., 2014). It consists of headphones, two sensors strapped to the ankles and a laptop with custom made software, which is able to detect the step relative to the beat.

APDM sensors were used to measure the spatiotemporal gait parameters (APDM wearable technologies Inc, Portland, OR, USA https://apdm.com/mobility/). These wearable inertial measurement sensors are strapped around the ankles, the wrists and placed on the sternum of the participants. They appeared valid and repeatable in healthy young adults for measuring gait speed, cadence, stance percent, swing percent, stride duration, stride length and step duration (Washabaugh, Kalyanaraman, Adamczyk, Claflin, & Krishnan, 2017). They were also sensitive and specific for detecting excessive gait variability in 205 persons with manifest or prodromal spinocerebellar ataxia. This study stated that "they are reliable and related to the severity of the disease, suggesting they may be useful as clinical trial performance outcome measures (Shah et al., 2021)".

Figure 2 provides a visualization of the equipment described above.

Figure 2: Experimental equipment

3.4 DESCRIPTIVE TEST AND MEASURES

Following tests were conducting during the descriptive testing session one: the Motricity Index scale (MI), Modified Ashworth scale (MAS), Timed Up and Go (TUG), Six-minute Walking test (6MWT), Scale for Assessment and Rating of Ataxia (SARA), Dynamic Gait Index (DGI), Edinburg Handedness Inventory (EHI) and the Nine hole peg test (NHPT) as motor testing's, the Cerebellar cognitive affective/Schmahmann syndrome (CCAS/SS) Scale as cognitive testing, the Montreal Battery of Evaluation of Amusia (MBEA) for measuring beat perception and the Activities-Specific Balance Confidence (ABC) scale, Modified Fatigue Impact (MFIS) Scale and the Hospital Anxiety and Depression (HADS) Scale as informative questionnaires.

In the section below, a description of each test is provided along with the way of interpreting the scores and if available, the validity and reliability of this measure tested in previous cohorts.

3.4.1 Motor testing

Motricity Index scale (MI)

The motricity Index scale is used to measure strength deficits in the upper and lower limbs. The validity and reliability has been established in persons with stroke (Lin, Arevalo, Harvey, Prabhakaran, & Martin, 2022). The maximal voluntary contraction over the whole range of motion is evaluated against the therapist resistance. For this study, only the muscles of the lower limbs are evaluated: ankle dorsiflexors, knee extensors and hip flexors. The maximal score for each muscle group is 33, which reflects a normal force.

Modified Ashworth scale (MAS)

The Modified Ashworth scale is used for measuring resistance against passive movement of a muscle and appears to have a good inter- and intra-rater reliability in children and adults with spasticity (cerebral palsy, stroke, traumatic brain injury, spinal cord injury and cerebral hypoxia) (Meseguer-Henarejos, Sánchez-Meca, López-Pina, & Carles-Hernández, 2018). In our study, the hamstrings, triceps surae and the quadriceps are evaluated and scored on a 0-4 scale. When the limb is fixed in flexion a score of 4 is given. When no resistance is felt during the whole range of movement a score of 0 is given.

Timed Up and Go (TUG)

This test is recommended to asses balance in PwCI by (Winser, Smith, Hale, Claydon, & Whitney, 2015). The TUG shows a good reliability and acceptable validity in persons with cerebellar ataxia due to multiple sclerosis (Winser et al., 2017). The participants are asked to get up from a chair, walk 3 meters and return to the chair. The time is measured and the average of three attempts was taken in this study. In frail elderly, a score of less than 10 seconds reflects an independent mobility (Podsiadlo& Richardson, 1991).

Six-minute Walking test (6MWT)

The 6MWT provides an estimate of walking ability in cerebellar ataxia (Marquer et al., 2014). The distance walked in 6 minute time is measured in meters and can be compared to normative value's for age, sex and body mass index (Beekman et al., 2014).

Scale for Assessment and Rating of Ataxia (SARA)

The SARA is the most common scale for assessment of ataxia. It's validity and reliability has been established in patients with spinocerebellar ataxia (SCA), "making it an appropriate primary outcome measure for clinical trials (Schmitz-Hübsch et al., 2006)". In 64 non-SCA patients with ataxia, the inter-rater (ICC 0.98) and intra-rater (ICC 0.99) reliability of the SARA was found to be high, as well as the internal consistency with a Cronbach's alpha of 0.97 (Weyer et al., 2007). The scale is composed of 8 subscales measuring gait, stance, sitting, speech, finger chase, nose-finger, fast alternating movements and heel-shin slide. The average of the left and right side is used for the scoring, with a total score ranging from 0 (no ataxia) to 40 (most severe ataxia). A disadvantage of this scale is that it does not measure oculomotor performance, which is a clinical feature in PwCI with the vestibulo-cerebellar syndrome (Cabaraux et al., 2021).

Dynamic Gait Index (DGI)

The DGI was developed by Shumway-Cook and Woollacott (1995) for the evaluation of gait, balance and risk of falling. The psychometric properties of this activity-level measurement has been investigated in 20 adults with ataxia (Reoli et al., 2021). The authors reported a high inter-rater (ICC 0.98) and test-retest (ICC 0.98) reliability and stated: "In terms of construct validity, we found significant correlations between the activity level DGI and

impairment level outcome measures (-0.81 for SARA; -0.88 with ICARS) (Reoli et al., 2021)". The DGI consist of eight domains: gait level surface, change in gait speed, gait horizontal head turn, gait vertical head turn, gait and pivot turn, step over obstacle, step around obstacle steps. They are each scored on a scale from 0 (severe impairment) to 3 (normal), with a best possible total score of 24 points.

Edinburg Handedness Inventory (EHI)

The EHI is a self-reported inventory that assesses hand preference for uni- and bi manual activities such as writing and drawing, throwing, and using daily life instruments as a toothbrush, a knife, or a spoon (Caplan& Mendoza, 2011). In this study, the 10-item short form of the EHI was used in order to determine the preferred hand of the participants for the tapping experiment.

Nine hole peg test (NHPT)

The NHPT assesses manual dexterity, which could be influencing the tapping task in this study. In 14 adults with cerebellar degeneration, the NHPT was correlated with ataxia severity (Barbuto, Mackenzie, Kuo, Kitago, & Stein, 2020). The participants have to put 9 sticks in holes and remove them back into the box as quickly as possible. The average time of two measurements is taken for each hand and higher times indicate a worse score. Normative values are available for this test, taking into account gender and age (Oxford Grice et al., 2003).

3.4.2 Cognitive testing

Cerebellar cognitive affective/Schmahmann syndrome (CCAS/SS) Scale

The CCAS/Schmanhmann's syndrome is one of the cerebellar syndromes described in the chapter of Cabaraux et al. (2021), which is characterized by impairments in executive function, spatial cognition, linguistic functions and affect regulation (Schmahmann& Sherman, 1998). The CCAS/SS Scale was developed by Hoche, Guell, Vangel, Sherman, and Schmahmann (2018) and validated for the assessment of CCAS/SS in PwCI. This scale measures semantic fluency, phonemic fluency, category switching, the digit span forward, the digit span backward, a cube draw and cube copy task, delayed verbal recall, similarities, go/no-go, and neuropsychiatric domains. A higher score reflects a better performance of the tests, with a maximum total score of 120 points. For each item a pass-fail threshold was set.

One failed test is seen as a possible diagnosis of CCAS/SS, two failed tests is a probable diagnosis of CCAS, and three failed tests is a definite diagnosis of CCAS/SS (Hoche et al., 2018).

3.4.3 Beat perception testing

Montreal Battery of Evaluation of Amusia (MBEA)

The Montreal battery of amusia (MBEA) is used is this study to determine the rhythm abilities of our participants, as according to Crosby, Chen, Grahn, and Patterson (2022) this could have an influence on synchronization ability. The review of Peretz, Champod, and Hyde (2003) concludes that "the MBEA has been shown a good sensitivity, reliability and validity in detecting amusia." The MBEA assesses six music processing components: scale, contour, interval, rhythm, metric, and music memory. For this study, only the 'Rhythm' subscale is used and scored on a scale of 0-15, with 15 being the best score. Validity and reliability of the subscale 'rhythm' on its own were not found.

3.4.4 Questionnaires

Activities-Specific Balance Confidence (ABC) Scale

The ABC scale measures the loss of balance confidence in activities of daily living. The scale was found to be internally consistent with the Falls efficacy scale and demonstrated a good test-retest reliability, convergent and criterion validity in elderly (Powell& Myers, 1995). The Canadian French version we are using in this study, was validated and shown to be reliable among 91 persons with stroke (Salbach, Mayo, Hanley, Richards, & Wood-Dauphinee, 2006). This 16-item questionnaire is scored on a 0-45 scale and with percentages. A higher score or percentage reflects in more confidence in the activities.

Modified Fatigue Impact (MFIS) Scale

The MFIS aims to assess the impact of fatigue on physical, cognitive and psychosocial functioning. A French version of the MFIS has been developed by Debouverie, Pittion-Vouyovitch, Louis, and Guillemin (2007) and has shown to be reliable and valid in a cohort of persons with multiple sclerosis. However, the short form (21 items) which we are using in this study has not been validated in French. Although the English version of the 21-item MFIS is wildly used in persons with multiple sclerosis, the study of Mills, Young, Pallant, and Tennant (2010) states that the overall score cannot be used as an outcome measure or a

selection tool. In our study, the 21-item MFIS is used as a purely informative questionnaire. The score ranges from 0-84 and the higher the score, the more fatigue the person experiences in daily life.

Hospital Anxiety and Depression (HADS) Scale

The HADS is a 14 item questionnaire developed for measuring anxiety (7 items) and depression (7 items) in hospital medial outpatient clinic (Zigmond& Snaith, 1983). The French version we are using in this study, was validated and shown to be reliable in the study of Roberge et al. (2013) which recruited 14.883 adults in primary care clinics in Quebec, Canada. The items are scored on a scale of 0-3. A higher score reflects greater complains in depression and anxiety. The cut-off score is 16/42 points for the total HADS, 7/21 for the HADS – depression subscale and 10/21 points for the HADS – anxiety subscale (Roberge et al., 2013).

3.5 EXPERIMENTAL OUTCOME MEASURES

Following measures were collected during the second and third experimental sessions: primary outcomes of synchronization during the finger-tapping and the walking paradigm and secondary outcomes of spatiotemporal gait parameters during the walking paradigm only. In the section below, they are described and their interpretation is discussed.

3.5.1 Primary outcome measures

Auditory-motor coupling or synchronization ability will be measured during the walking and the tapping experiment by detecting the step/tap relative to the beat from the auditory stimuli and by this calculate following synchronization measures:

- *"Relative phase angle* (measured in degrees): This is a measure of the timing of the footfall relative to the closest beat. The relative phase angle can be expressed as either a positive (footfall after the beat) or a negative (footfall before the beat) angle in degrees *(Moumdjian et al., 2018)".*
- *"Resultant vector length* (expressed as a value from 0 to 1): This measure expresses the coherence or stability of the relative phase angles over time. If the distribution of the relative phase angles over time is steep, it results in a high resultant vector length (max value 1). If the distribution of the relative phase angle over time is not steep but broad or multimodal, it results in a low resultant vector length (min value 0) (Moumdjian et al., 2018)".
- "*Inter-beat deviation (IBD) or tempo matching accuracy* (measured in ms): This parameter indicates the extent to which the overall tempo of the footfalls matches the overall tempo of the beats (Moumdjian et al., 2018)". A value close to zero means that the footfall matches the beat, a value further away from zero means more overall deviation from the beat (Moumdjian et al., 2018).

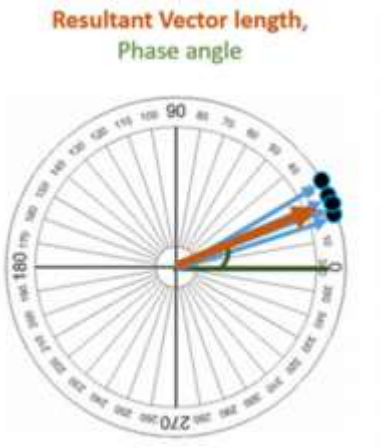

Figure 3: Visualization of PA and RVL

Figure 3 visualizes the '*relative phase angle*' and the '*resultant vector length*'. The beat is set on 0°. The black points stand for the distance in degrees of the steps from the beat. Reprinted with permission from "Entrainment and Synchronization to Auditory Stimuli During Walking in Healthy and Neurological Populations: A Methodological Systematic Review" by L. Moumdjian, J. Buhmann, I. Willems, P. Feys, and M. Leman, 2018, *Front Hum Neurosci, 12*, 263.

A robust cut off value to determine if a person is able to synchronize has not been established. However, in the study of Buhmann, Desmet, Moens, Van Dyck, and Leman (2016) the result of vector length (RVL) was found to be mostly above 0.74 in 30 healthy participants who walked at their preferred walking cadence on tempo-matched music. As participants in our study will be asked to synchronize (instructed or intended synchronization) and the participants in the study of Buhmann, Desmet, et al. (2016) were not instructed to synchronize to the beat, it is not completely applicable to our experiment. Still, the value can be used as indication, just like in the study of Moumdjian et al. (2019).

3.5.2 Secondary outcome measures

Following spatiotemporal gait parameters will be collected: cadence in steps per minute (step/min), double limb support in percentage of the total gait cycle (%GC), speed in meters per second (m/s), lateral step variability centimeters (cm), step time in seconds (s) and stride length in meters (m). The Coefficient of Variance (CV) was used in the study of Schniepp et al. (2014) for determining the variability of stride time, stride length and base of support in patients with cerebellar ataxia. The CV is the ratio of the standard deviation to the mean. Higher scores reflect more variability in the gait parameter. In this study, the CV will be used to calculate the variability of double limb support (DLS%), speed, step time and stride length.

3.6 DATA ANALYSIS

The demographical data and the baseline gait parameters between PwCI and HC's were compared with following non-parametrical statistical tests. For continuous data, the assumption of normal distribution was checked with a Shapiro-Wilk test/Kolmogorov-smirnov test and homoscedasticity of the groups with a Brown- Forsythe test. If these assumptions were both met, a Wilcoxon rank-sum test and a 2 sample test was used. If data was not normally distributed, but variances were equal, only a Wilcoxon rank-sum test was used. If data was normally distributed but variances were unequal, a Welch test was used. For the categorical outcome measure 'age' the fisher's exact test or a Pearson test was used depending on the average cell count (<5 use fishers' exact test).

For analysis of the synchronization parameters and the gait parameters in the different conditions, a mixed model analysis of variance (ANOVA) was used with forward model building. The random factor was the participant undergoing repeated measures. The fixed between-cluster factors was the group (PwCI or HC's). The fixed within-cluster factors were type of stimuli (music or metronomes) and tempi [-12%, -8% -4%, 0%, +4%, +8%, + 12%]. The level of significance was set on alpha 0.05. A Tukey test was conducted as a post hoc test to correct the p-value for multiple comparisons. Assumptions of normality and homoscedasticity were checked with residual graphical plots for each outcome measure. As this is a pilot study with a low number of participants, all results should be interpreted with caution.

All the data was analyzed using the statistical program JMP Pro 16 (SAS, USA). For the preprocessing of the average relative phase angle (=directional data) circular statistics were used (Philipp, 2009).

When data of all participants will be available, a factor analysis will be conducted for the SARA and the DGI, in order to investigate the influence of ataxia and dynamic balance impairment synchronization ability and gait parameters.

4 RESULTS

Five PwCI and five HC's completed the experiment in this study. In the following section, the demographic information, the diagnosis and clinical picture including an MRI, the descriptive tests and the results of the primary and secondary outcome measures assessed during both experiments are presented. In order to refer to the participants individually, the HC's and the PwCI are each given the anonymous codes 1-5.

4.1 DEMOGRAPHICS

The demographical information was fully available for the five PwCI, but only for three out of five healthy controls. This demographic information is presented in Table 1. No significant differences (alpha < 0.025 because of two tailed hypothesis) were found across the groups in terms of age, gender, height and weight. PwCI 2 and 4 still worked as a kindergarten teacher and a pharmaceutics assistant and HC 3 and 4 were doing a PhD. Other participants were retired. Participants had no musical experience at the time of entering the study, except for PwCI 3 who had been in a choir years ago and one HC 4 who played guitar and sang.

Table 1: Demographic information

Demographics	*PwCI (N=5)*	*HC (N=3)*	*Wilcoxon rank-sum test and two sample t-test*
Age (years)	64,6 (SD 7.23)	53 (SD 21.63)	ns
Gender (M/F)	F3/M2	F1/M2	ns°
Height (cm)	169 (SD 3.32)	175.3 (SD15.88)	ns
Weight (kg)	78 (SD 3.94)	77.67 (SD19.55)	ns

Abbreviations: PwCI; persons with cerebellar impairments, HC; healthy controls, F; female, M; male, SD; standard deviation, ns; non-significant, ° fisher's exact test

4.2 DIAGNOSIS AND CLINICAL PICTURE

Table 2 presents the diagnosis, the date of diagnosis, the MRI findings, the clinical presentation and the current prescribed treatment of the PwCI. The diagnosis of the five PwCI were two cerebellar strokes, one hereditary degenerative progressive ataxia (SCA type 6), a mutation in the CACNA1A gene in combination with spastic paraplegia type 7 and a left middle cerebellar peduncle lesion for which the etiology was inconclusive. All patients were diagnosed relatively recent as their time from diagnosis did not exceed 5 years. On the intake conversation/examination two patients reported having cognitive symptoms, two patients presented with vertigo and/or dizziness and all patients reported problems with balance/postural control. Based on the clinical presentation, an estimate was made of the presence of cerebellar syndromes described by Cabaraux et al. (2021). Current management was mainly with medication specific for their cerebellar condition and their vascular or neurological comorbidities. A more detailed description of the MRI lesions linked to the clinical presentation and the motor and cognitive testing is found in the section *'4.6 Reporting on individual cases'.*

Table 2: Diagnosis and clinical picture

Participant	*Diagnosis*	*MRI*	*Age, gender*	*Date of diagnosis*	*Other info*	*Clinical presentation*	*Cerebellar syndrome*	*Prescribed treatment*
1	Etiology of lesion not conclusive: ischemic, or inflammatory or neuropathic	Left middle cerebellar peduncle lesion	69 F	02/2020	None	Nystagmus, sensibility loss of L side of face, pain in the face with touch and chewing, issues with equilibrium and vertigo	VCS	Vestibular physiotherapy, no medication for the lesion, Lyrica for her facial pain
2	Cerebellar stroke	Left posterior cerebellar stroke (Superior cerebellar artery territory)	62 F	11/2018	Left frontal anterior lesion ; Epilepsy	Instability and balance, left slight ataxia, cognitive symptoms	CMS, CCAS/SS	Medication for epilepsy (depakine), to sleep (zopidem, alprazolam), and for her cardiovascular condition
3	SCA type 6	Global cerebellar atrophy predominantly cerebellar vermis	65 M	Around 2017	None	Instability and balance issues, falls	CMS	Fampyra (for gait), AHM
4	SPG 7 and 2 mutations in the CACNA1A gene	Normal	54 F	Around 2018	Mechanical troubles (hip issue)	Balance, equilibrium and coordination issues, cognitive deficits, narcolepsy	CMS, CCAS/SS	Under Diamox (for ataxia), and lioresal for spasticity (?)
5	Cerebellar stroke	Right posterior paravermis PICA (posterior inferior cerebellar artery) stroke	73 M	09/2019	None	Postural instability and vertigo/dizinness	CMS, VCS	Antidepressive medication (fluoxetine), Medication for RLLS (pramipexole), AHM

Abbreviations: M; male, F: Female, R; right, L; left, SCA: spinocerebellar ataxia, VCS: vestibulo-cerebellar Syndrome, CCAS/SS: cerebellar cognitive/affective syndrome/Schmahmann's syndrome, CMS: cerebellar motor syndrome, SPG 7: spastic paraplegia type 7, AHM; anti-hypertensive medication, RLS; Restless legs syndrome

4.3 DESCRIPTIVE TESTS AND MEASURES

Table 3 presents the results of the descriptive measurements for the PwCI. There was missing data for the questionnaires of participant 1.

No major strength deficits or spasticity was detected in any PwCI. The TUG scores were good for most PwCI, ranging from 7.6 to 14.9 seconds. Overall, the SARA scores were relatively good and participants showed deficits in the 'fast alternating hand movements' subscale (slightly irregular in participant 2, 3 and 4) and most of all in the 'gait' subscale, with a worse score of 3/8 for participant 3 (= considerable staggering, difficulties in half-turn, but without support). Variable scores on the DGI ranging from 15-24/24 were observed. The manual dexterity measured with the NHPT was good for participant 1, 2 and 5 and was worse than the normative value for participant number 3 and 4. All participants scored well on the MBEA rhythm scale meaning no amusia was present. The ABC scale showed markedly reduced confidence in balance during daily life activities for participants 2, 3 and 4. The four PwCI who filled in the MFIS experienced a certain amount of fatigue in daily life with a total score ranging from 58 to 66/84. According to the cut off scores of the HADS (Roberge et al., 2013), participant 2 and 3 experienced anxiety and participants 2, 3 and 4 experienced depression. The total HADS score was above the cut off value of 16/42 for three of the four patients. Participant number 5 was the only one who was treated with antidepressant medication for this, even though he did not cross not cross the total cut off score for anxiety nor depression.

Table 3: Descriptive testing

	Measures	Subscales	Participants				
			1	2	3	4	5
Motor testing	*MI (0-33)*	*Dorsiflexors*	L33 R33	L25 R33	L33 R33	L33 R25	L33 R33
		Knee extensors	L33 R33	L25 R33	L25 R33	L33 R25	L25 R33
		Hip flexors	L25 R33	L25 R33	L25 R33	L33 R33	L25 R33
	MAS (0-4)	*Hamstrings*	0	0	0	0	0
		Triceps surae	0	0	0	0	0
		Quadriceps	0	0	0	0	0
	TUG (sec)		10,1	7,6	14,5	14,9	9,6
	6MWT (meters)		470	473	334	486	504
	SARA (0-40)	*Gait (0-8)*	0	1	3	2	1
		Stance (0-6)	0	0	2	0	1
		Sitting (0-4)	0	0	0	0	0
		Speech disturbance (0-6)	0	0	2	1	0
		Finger chase (0-4)	0	0,5	0	0	0
		Nose-finger test (0-4)	0	0	1	0	0
		Fast alternating hand movement(0-4)	0	0,5	1	1	0
		Heel-shin slide (0-4)	0	0	1	1,5	0
		***TOTAL** (0-40)*	0	2	10	5,5	2
	DGI (0-24)	*Gait level surface (0-3)*	3	3	2	3	3
		Change in gait speed (0-3)	3	3	1	3	3
		Gait horizontal head turn (0-3)	3	3	2	2	3
		Gait vertical head turn (0-3)	3	2	2	2	3
		Gait and pivot turn (0-3)	3	3	2	3	3
		Step over obstacle (0-3)	3	3	2	2	3
		Step around obstacle (0-3)	3	3	2	2	3
		Steps (0-3)	3	3	2	2	3
		***TOTAL** (0-24)*	24	23	15	19	24
	EHI (L/R)		R	R	R	R	R
	NHPT (sec)	*Left*	*	27,1	42	31,8	22,8
		Right	*	22,4	33,7	37,3	25,9
Cognitive testing	*CCAS/SS scale*	*Semantic fluency (0-26)*	26	26	25	11	20
		Phonemic fluency (0-19)	14	15	18	5	7
		Category switching (0-15)	15	12	15	11	12
		Verbal registration /	/	/	/	/	/
		Digit span forward (0-8)	6	5	6	5	5
		Digit span backword (0-6)	4	3	6	4	4
		Cube (draw) /	/	/	/	/	/

		Cube (copy) (0-15)	12	15	15	10	15
		Verbal Recall (0-15)	11	15	12	7	13
		Similarities (0-8)	8	8	8	7	8
		Go-No-Go (0-2)	1	0	2	1	2
		Affect (0-6)	6	4	5	4	5
		***TOTAL** (0-120)*	103	103	112	65	91
		***PASS - FAIL** (0-10)*	0	1	0	6	2
Beat perception	*MBEA Rhythm*		14	15	13	12	15
Questionnaires	*ABC scale*	***TOTAL** (0-45)*	*	29	20	22	40
		PERCENTAGE %	*	64.44	44.44	48.88	88.88
	MFIS	*Physical (0-36)*	*	23	31	27	27
		Cognitive (0-40)	*	35	21	27	28
		Psychological (0-8)	*	8	6	5	6
		TOTAL (0-84)	*	66	58	59	61
	HADS	*Anxiety (0-21)*	*	16	12	6	7
		Depression (0-21)	*	16	8	12	5
		TOTAL (0-42)	*	31	20	18	12

Abbreviations: MI; Motricity index, MAS; Modified Ashworth Scale, TUG: Timed Up and Go, 6MWT; six-minute walking test, SARA; Scale for Assessment and Rating of Ataxia, DGI; dynamic gait index, EHI; Edinburg Handedness Inventory, NHPT; Nine hole peg test, CCAS/SS scale; Cerebellar cognitive affective/Schmahmann syndrome Scale, MBEA; Montreal Battery of Evaluation of Amusia, ABC; Activities-Specific Balance Confidence Scale, MFIS; Modified Fatigue Impact Scale, HADS; Hospital Anxiety and Depression Scale, L; left, R; right, *; missing data, /: item is not to be scored

4.4 PRIMARY OUTCOME MEASURES

In the following section, results of the primary outcome measures are presented. First for the tapping experiment and then for the walking experiment. There was missing data in participant number PwCI 4, HC 2 and HC 8 for the finger-tapping experiment which accounted for 15% of all tapping data. The data of the walking experiment was complete. Outliers were removed by examining the box plots and figures in JMP. In the figures, each error bar was constructed using 1 standard error from the mean.

4.4.1 TAPPING to music and metronomes at various tempi – synchronization

In order to answer the research question: "Can PwCI synchronize their finger-tapping to rhythmic auditory stimuli at various tempi?' synchronization measures (RVL, PA and IBD) were compared between HC's and PwCI. Further, the X variables stimuli (metronomes and music) and tempi [-12%, -8% -4%, 0%, +4%, +8%, + 12%] were analyzed to see if they had an effect on the synchronization measures.

Resultant vector length (RVL): As seen in figure 4, the mean RVL was significantly higher (P=0.0071) in HC (mean RVL 0.92) than in PwCI (mean RVL 0.8). Four out of five PwCI had an RVL of above 0.75, which means PwCI could still synchronize their tap to the beat. Overall the RVL was significantly lower in music compared to metronomes (P= 0.0314), and the interaction with group was almost significant (P= 0.0845). Multiple comparisons with a post hoc Tukey tests showed that in PwCI, the RVL was significantly lower in music compared to metronomes (P= 0.0213) while this was not the case in HC's (P= 0.9925). There was no significant (P= 0.5298) influence of tempi on RVL, nor its interactions with group and stimuli.

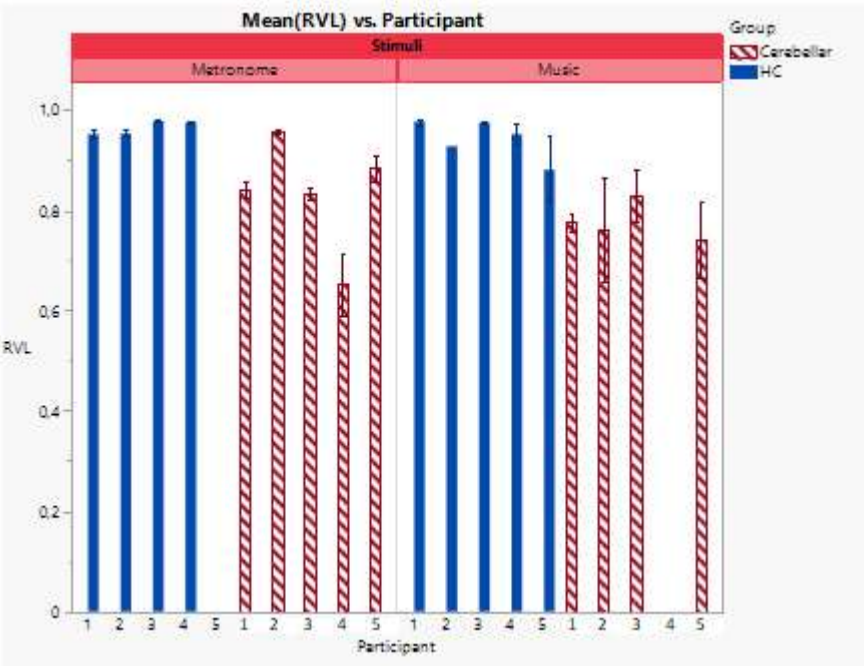

Figure 4: Resultant of Vector Length - tapping

Relative phase angle (PA): The PA was significantly different for type of stimuli (P< 0.0001). Figure 5 shows that most of the taps come before (negative value) the beat when tapping to metronomes in PwCI and HC's. This suggests that both groups are predicting the beat and entrainment is happening. When tapping to music the PA is less consistent and shows some positive value's, which means entrainment is less present in both groups than in metronomes.

Group and tempo had no significant influence on the PA, but their interaction was significant (P= 0.0479). However, no significant pairwise comparison was found when corrected with the post hoc Tukey test.

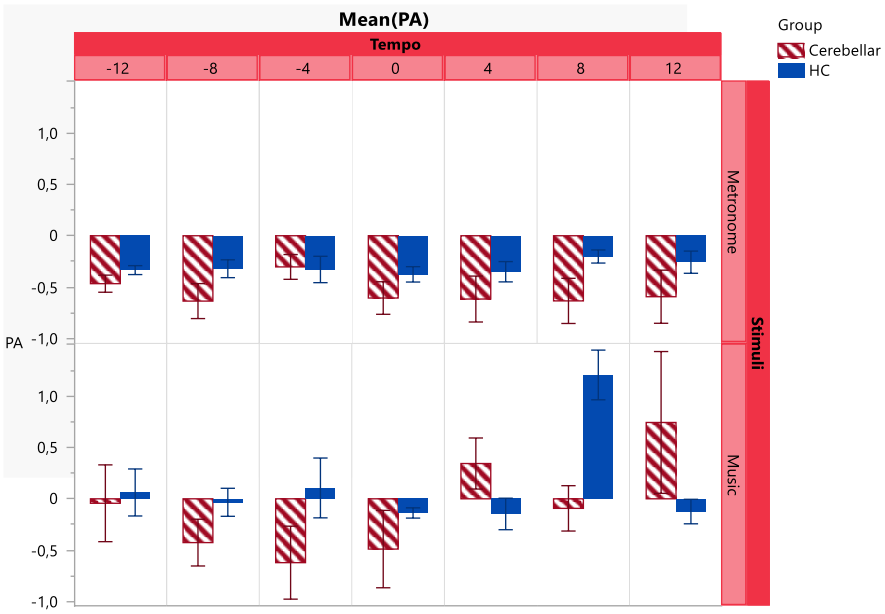

Figure 5: Phase Angle – tapping

Inter-beat deviation (IBD) or tempo matching accuracy: There was a significant interaction effect between group and stimuli. A Tukey pairwise comparison showed that the IBD was further away from zero when tapping to music then when tapping to metronomes (P= 0.009) in PwCI but in the HC's.

4.4.2 WALKING to music and metronomes at various tempi - synchronization

In order to answer the research question: “Can PwCI synchronize their steps to rhythmic auditory stimuli while walking at various tempi?’ synchronization measures (RVL, PA and IBD) were compared between HC’s and PwCI. Further, the X variables stimuli (metronomes and music) and tempi [-12%, -8% -4%, 0%, +4%, +8%, + 12%] were analyzed perceive their effect on the synchronization outcome measures. Additionally, the Resultant Vector length (RVL) was compared between the tapping and the walking experiment.

Resultant of Vector length (RVL): The mean RVL was significantly higher (P< 0.0001) in HC (mean RVL 0.9) than in PwCI (mean RVL 0.5) in the walking experiment. Only 2 out of 5 PwCI had an mean RVL above 0.75. Figure 6 presents the comparison with the tapping experiment. The RVL was significantly lower when walking music and metronomes at different tempi (P< 0.0001) in PwCI compared to tapping. The RVL did not differ between the tapping and walking experiment for HC’s (P= 0.8100).

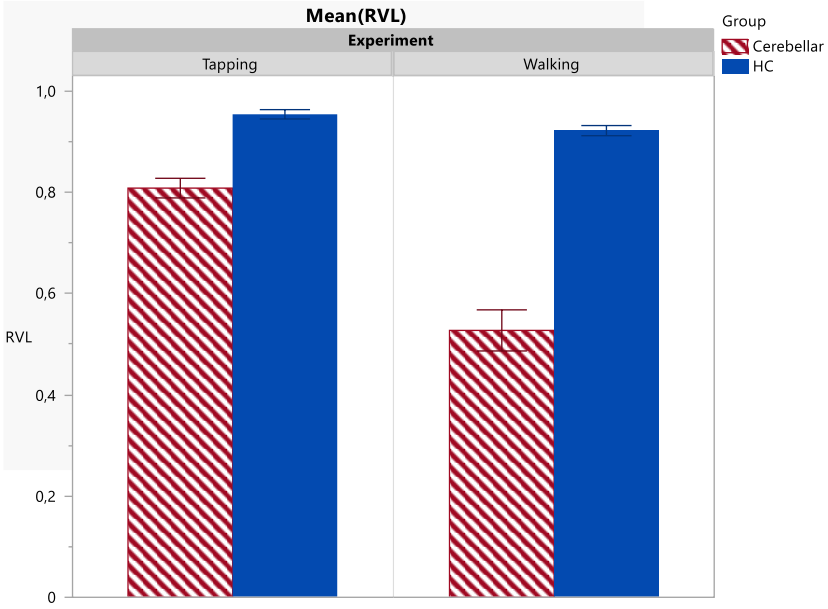

Figure 6: Resultant of Vector Length - tapping vs walking

The RVL was significantly different for music and metronomes (P= 0.0003), with music having a lower RVL according to the post hoc Tukey test for both groups. In figure 7 the significant interaction between tempi and group (P= 0.0033) is clarified. In PwCI, the RVL of the +12% tempi was significantly different from the -8%, -4% (both P< 0.0001) and 0% tempi (P= 0.0156) according to the post-hoc Tukey test.

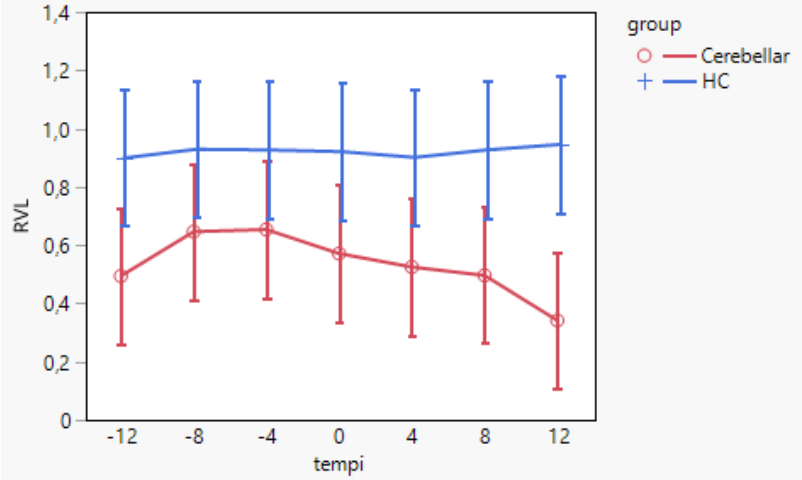

Figure 7: Resultant of Vector Length - tapping

<u>Relative phase angle (PA):</u> The tempi was the only significant variable influencing the PA (P= 0.0001). Group (P= 0.1331), group*tempi (P= 0.1057) and stimuli (P= 0.0935) were almost significant. Figure 8 shows that the footfall comes mostly after the beat in in both groups and that this trend is increased when walking at higher tempi, especially in PwCI. This suggest that participants have more difficulty to anticipate to the beat at higher tempi especially the PwCI. The influence of tempi seems to be more variable with music than with metronomes, although this interaction was not significant (P= 0.5116).

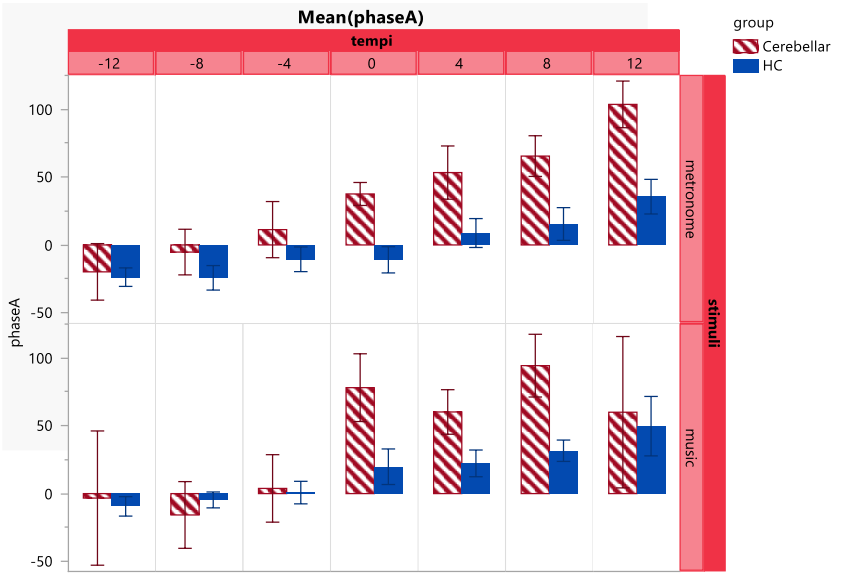

Figure 8: Phase angle - tapping

Inter-beat deviation (IBD) or tempo matching accuracy: There was a significant effect of tempi (P= 0.0001) an the interaction of group*tempi (P= 0.0001) on the IBD. Figure 9 clarifies that the IBD of HC's is close to zero, which means that the overall footfall matches the overall tempo of the beat. PwCI deviate more from the beat especially at high and low tempi. Pairwise comparisons showed a significant difference for the PwCI between tempi -4/+8, -4/+12, -8/+4, -8/+8, -8/+12 and 0/+12% and not for HC's, so both groups reacted differently to the tempi. Both groups did react the same way to stimuli, since participants their IBD was further away from zero with music than with metronomes (P= 0.0074) and no group interaction effect was present.

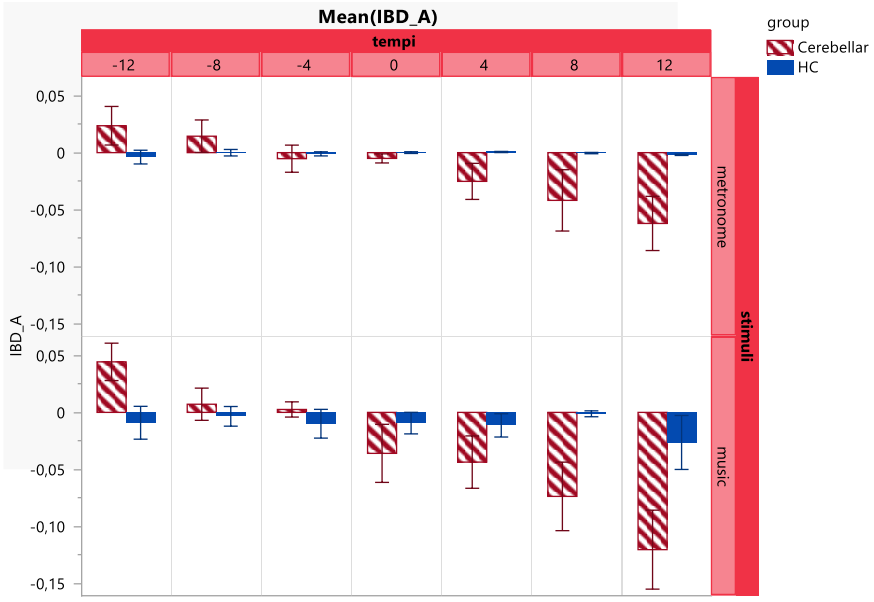

Figure 9: Inter-beat deviation - tapping

4.5 SECONDARY OUTCOME MEASURES: WALKING TO MUSIC AND METRONOMES AT VARIOUS TEMPI

In the following section, the results of the spatiotemporal gait parameters are presented. First, the baseline walking in silence for both groups were analyzed. Secondly, the difference between the gait parameters of the baseline and the conditions was taken for each value and the influence of the x-variables auditory stimuli (music or metronomes), all tempi and group were analyzed. The data from the spatiotemporal gait parameters was analyzed on for five PwCI and four HC's. HC number 2 was left out of the gait parameter analysis because baseline walking parameters were missing.

4.5.1 Baseline – spatiotemporal gait parameters

The baseline gait parameters when walking overground in silence for three minutes are presented separately for PwCI (Table 4) and for HC's (Table 5).

Table 4: Baseline spatiotemporal gait parameters - PwCI

PwCI	*Cadence (step/min)*	*Double Limb Support (%GC)*	*Double Limb Support CV*	*Speed (m/s)*	*Speed CV*	*Lateral Step Variability (cm)*	*Step time (s)*	*Step time CV*	*Stride Length (m)*	*Stride Length CV*
1	107,12	21,28	4,72	1,07	4,21	4,76	0,56	1,79	1,20	2,50
2	104,82	24,86	6,07	1,05	4,76	8,90	0,58	3,48	1,21	2,49
3	101,87	26,14	8,53	0,77	11,04	5,65	0,59	5,93	0,91	7,18
4	111,33	25,21	7,20	0,96	7,85	6,86	0,54	3,70	1,03	5,34
5	103,25	27,34	3,62	0,93	4,30	4,90	0,58	2,59	1,08	3,24
M	105,67	24,96	6,03	0,96	6,43	6,21	0,57	3,50	1,08	4,15
SD	± 3.71	± 2.27	± 1.95	±0.12	±2.98	± 1.72	±0.02	±1.56	± 0.16	± 2.05

PwCI: Persons with cerebellar impairments, CV; Coefficient of variance, %GT; % gait cycle, M; mean, SD; standard deviation, m; meters, s; seconds, min; minute.

Table 5: Baseline spatiotemporal gait parameters - HC's

HC	*Cadence (step/min)*	*Double Limb Support (%GC)*	*Double Limb Support CV*	*Speed (m/s)*	*Speed CV*	*Lateral Step Variability (cm)*	*Step time (s)*	*Step time CV*	*Stride Length (m)*	*Stride Length CV*
1	100,85	23,13	5,40	1,12	2,69	4,30	0,60	1,68	1,33	2,64
3	115,70	17,58	3,76	1,31	3,05	5,15	0,52	1,92	1,36	2,57
4	108,69	20,62	3,15	1,08	3,72	3,81	0,56	1,80	1,19	2,53
5	111,54	20,86	5,68	1,09	4,13	5,31	0,54	1,85	1,18	4,68
M	109,19	20,55	4,50	1,15	3,40	4,64	0,55	1,81	1,26	3,11
SD	± 6.26	± 2.28	± 1.24	± 0.2	±0.65	± 0.71	±0.03	± 0.1	± 0.09	± 1.05

HC; healthy controls, CV; Coefficient of variance, % gait cycle, M; mean, SD; standard deviation, m; meters, s; seconds, min; minute.

Statistical test were performed to determine differences across the groups. They were mostly non-parametric due to the small number of observations (PwCI N=5; HC N=4). The assumption of homoscedasticity was met for all gait parameters. All data was normally distributed except for speed and speed variability. Thus, a Wilcoxon rank-sum test and a two sample t test was used, except for the above mentioned outcomes where only a Wilcoxon rank-sum test was used.

The average walking speed was 0.955 (SD 0.119) for PwCI and 1.1475 (SD 0.12) for HC's. The speed was significantly lower (rank-sum p= 0.0143) in PwCI. The speed variability was 6.43 (SD2.98) in PwCI and 3.4 (SD 0.64) in HC's, which was significantly lower in HC's (rank-sum p= 0.0143). The average DLS% was significantly higher in PwCI (rank-sum p= 0.0275; t-test p=0.0125), with a mean of 24.96 (SD2.27) compared to a mean of 20.54 (SD 2.28) in the HC group.

No significant differences were found across groups for cadence, double limb support variability, lateral step variability, step time, step time variability, stride length stride length variability. However, when looking at graphical perspective (see figure 10), the stride length seems to be shorter in PwCI (rank-sum p=0.1416; t-test p=0.0234), step time variability is higher in PwCI (rank-sum p=0.0864; t-test p=0.0366) and the lateral step variability seems to be higher in PwCI (rank-sum p=0.1416; t-test p= 0.0582).

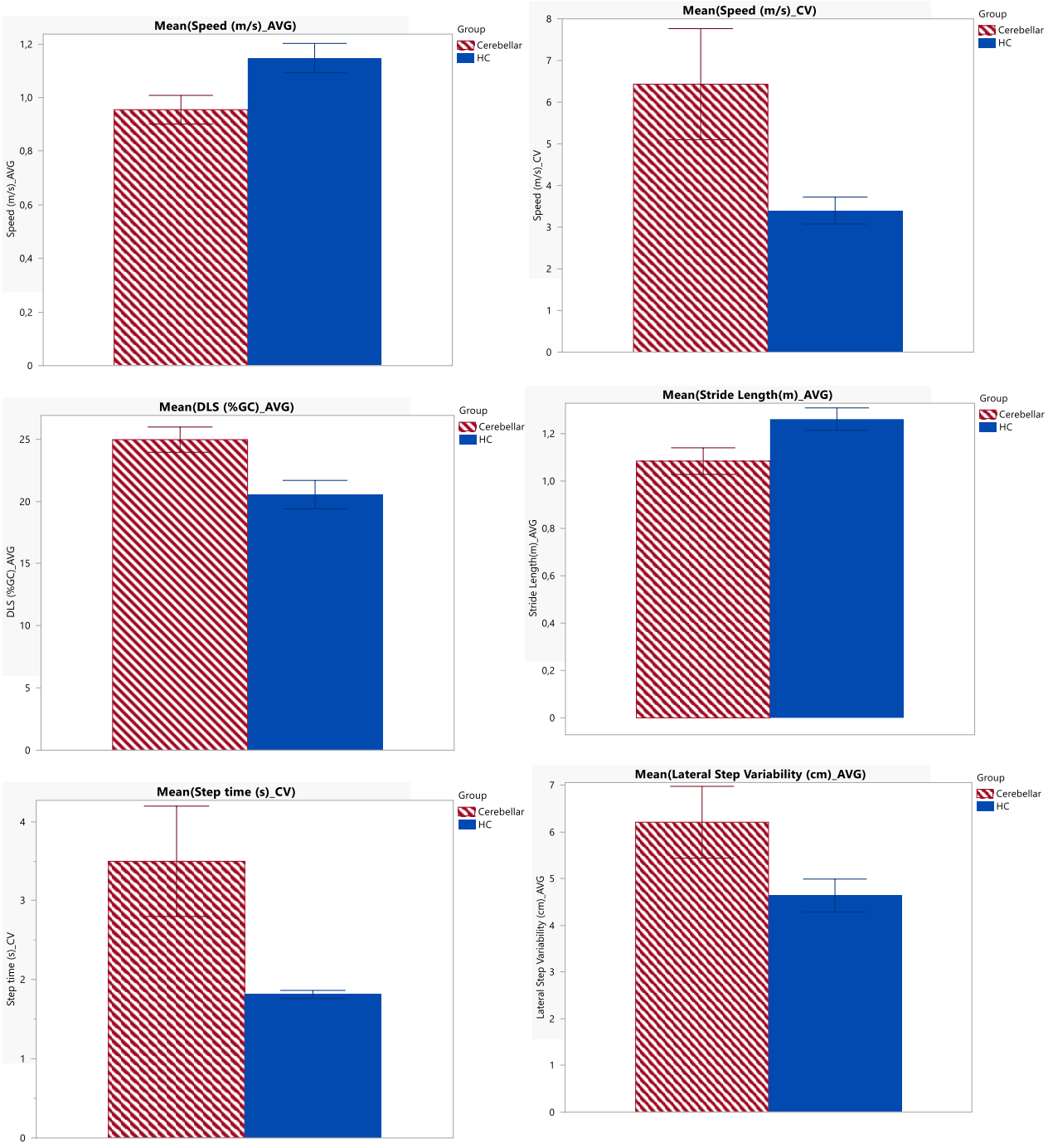

Figure 10: Baseline walking parameters

4.5.2 Difference conditions with baseline – spatiotemporal gait parameters

In order to answer the research question: "What is the implication of instructed auditory-motor coupling on gait parameters during walking to rhythmic auditory stimuli (tics in metronomes or beats in music) at different tempi [-12%, -8% -4%, 0%, +4%, +8%, + 12%]?", the difference between the baseline walking measurement and the condition (=stimuli X, tempo X) was taken (condition – baseline). Value's above zero indicate a higher absolute number of the condition than the absolute baseline measure. For example, a positive number for cadence indicates that participants walked at higher cadence in that condition than in their own baseline walking measurement.

In the following section, the effect of the fixed X-variables: tempi, stimuli and group and their interactions with each other are discussed for each gait parameter.

Cadence (step/min): The effect of tempi and the interaction group*tempi was both significant (P< 0.0001). In figure 11 we see that the cadence decreases at lower tempi and increases at higher tempi compared to baseline. The increase of cadence at higher tempi was higher for HC's then for PwCI, as the pairwise comparison with a post-hoc Tukey test was significantly different between the groups at tempo +12% (P= 0.0210).

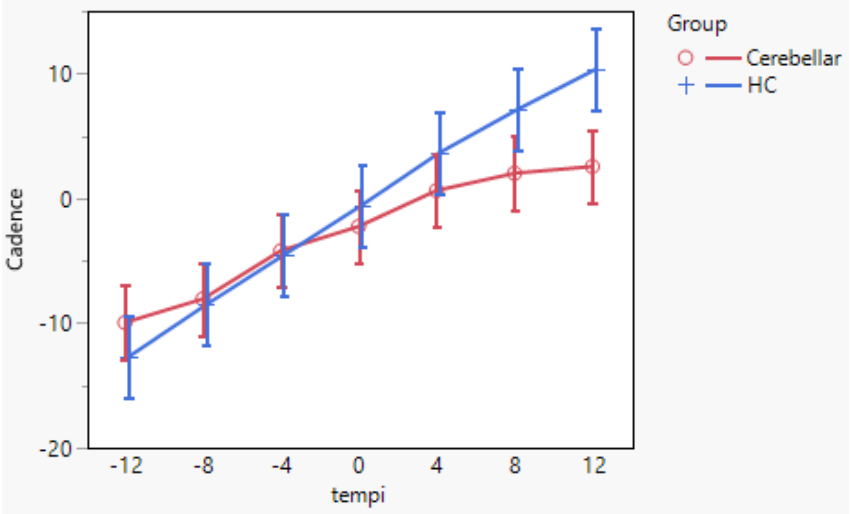

Figure 11: Cadence (step/min) - difference (condition-baseline)

The effect of stimuli was almost significant (P= 0.0883). In PwCI, the cadence seems to increase more with metronomes at higher tempi than with music at higher tempi. Overall, the cadence is further from the baseline across tempi with metronomes (see figure 12). This could mean that participants were better able to adjust their cadence to higher and lower tempi with metronomes than with music.

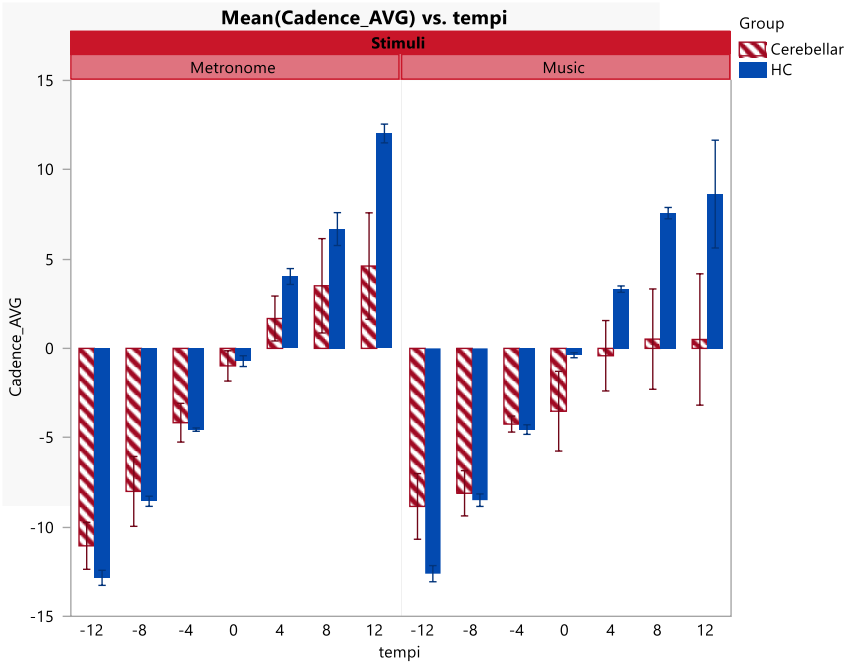

Figure 12: Cadence (step/min) - difference (condition-baseline)

Speed (m/s): was significantly different across tempi and the interaction effect tempi*group was also significant (both P< 0.0001). The HC's increased their speed above their baseline value at higher tempi, while the speed of PwCI stayed below their baseline value at all tempi. In figure 13 we see that with metronomes the speed of PwCI still follows the tempi (except for +12%), whereas with music they have more difficulty adapting their speed to the tempi.

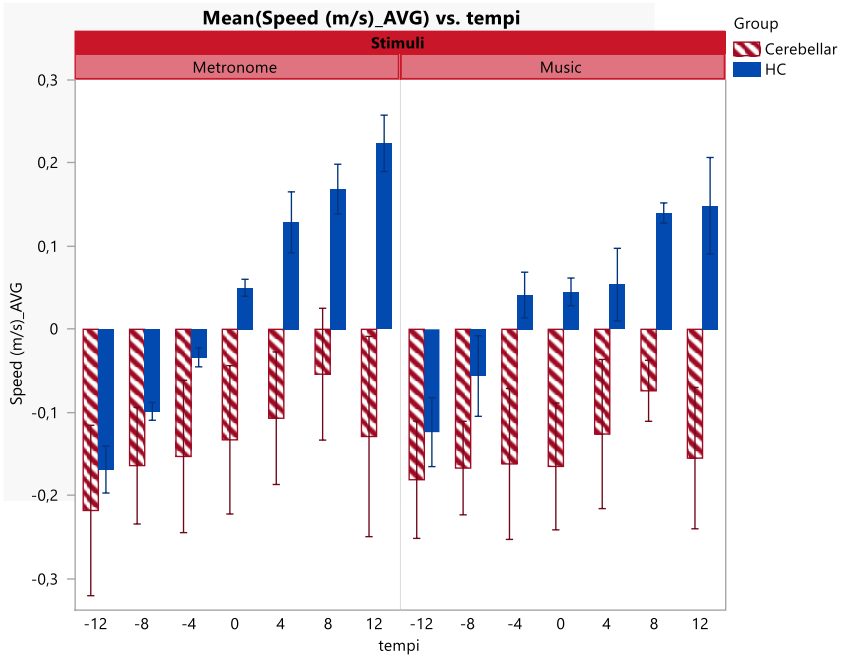

Figure 13: Speed (m/s) - difference (condition-baseline)

The speed variability (CV) was not significant for any X variable, although graphicly speed of the PwCI seem to be more variable than of HC, as was seen in the baseline analysis.

Double Limb support (%GC): There was a significant difference between the HC and the PwCI regarding the DLS% (P= 0.0196). In PwCI, the mean difference of DLS% was a value above zero for all tempi, which means the DLS% was higher when walking to auditory stimuli at various tempi compared to the baseline measurement (see figure 14). Overall, the effect of tempi was significant (P= 0.0001). According to the post hoc Tukey test, nine pairwise comparisons were significant (-12/4, -12/8, -12/12, -8/4, -8/8, -8/12, -4/8, -4/12, 0/8). However, the interaction between group and tempi was also significant (P=0.0041). As seen in figure 14, the DLS% increases at lower tempi and decrease at higher tempi for HC's but not for PwCI. The type of stimuli and other interactions were not significant.

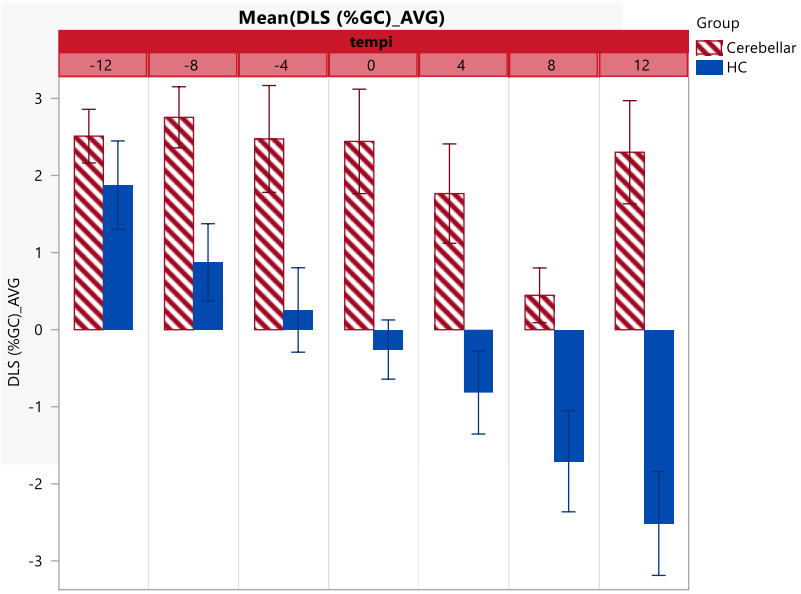

Figure 14: Double limb support (%GT) - difference (condition-baseline)

Double Limb support (%GC) variability (CV): The DLS% variability was above zero in all conditions, meaning that the DLS% variability was higher in the all the conditions than at the baseline measurements for both groups (see Figure 15). The pairwise comparisons for tempi showed only a significant difference between the condition at tempo -12 and 4% (P=0.0262). The effect of stimuli alone was also significant (P=0.0220), with music having a higher DLS% than metronomes across all tempi. There were no significant or graphicly valuable group or interaction effects present.

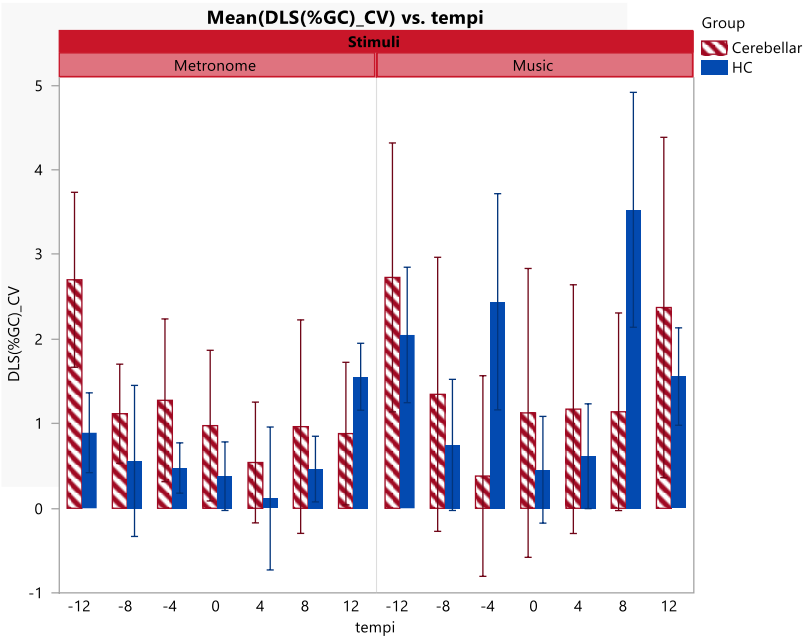

Figure 15: Double limb support variability (CV) - difference (condition-baseline)

Lateral step variability (cm): There was no significant influence of any X variable. Graphicly (figure 16), we see a decrease in lateral step variability in all conditions for the PwCI, especially with the metronomes. The interaction of group with stimuli was almost significant (P= 0.0593), meaning that the groups possibly react differently to music and metronome stimuli.

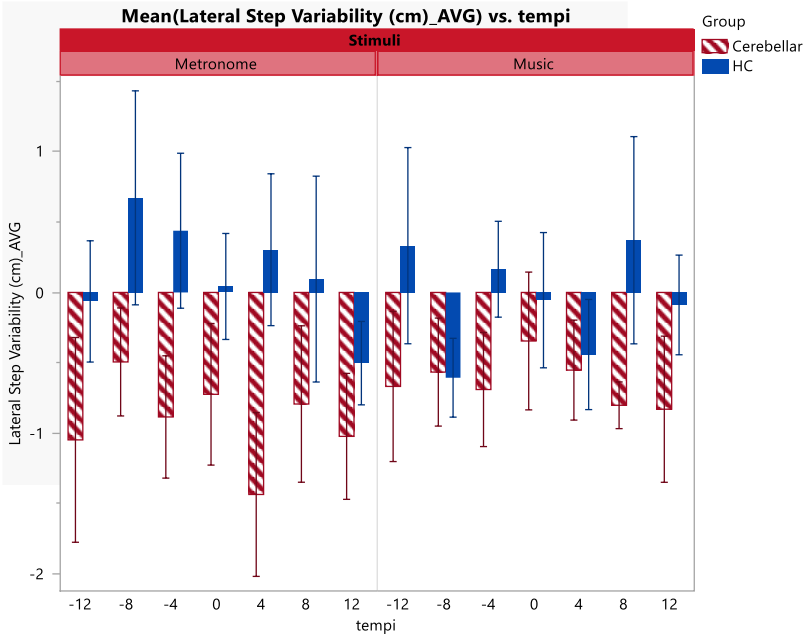

Figure 16: Lateral step variability (cm) - difference (condition-baseline)

Step time (s) significantly (P< 0.0001) increased with lower tempi and decreased at higher tempi (see figure 17). All pairwise comparisons were significant for the tempi for the two groups together, with the exception of +4/+8 and +8/+12. A significant interaction between group and tempi was present (P< 0.0001). More than half of the 94 post-hoc Tukey pairwise comparisons were significant. Thus, at higher tempi the decrease in step time was less for PwCI compared to the HC's. This is in accordance with the gait speed which was higher in HC's when walking at higher tempi compared to PwCI.

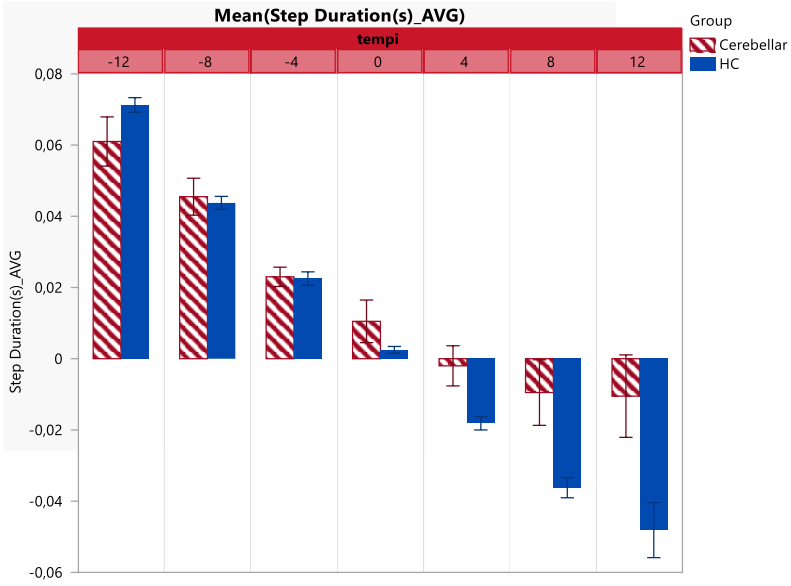

Figure 17: Step time(s) - difference (condition-baseline)

Step time variability (CV): The positive value on the y axis shows that the conditions had a higher step time variability when walking to auditory stimuli compared to the baseline measurement. The tempi had a significant influence on step time variability. Pairwise comparisons show a lower step time variability at -4% compared to -12% (P= 0.0394) and +12% (P= 0.0153). In figure 18 we see that the -4% has the lowest mean step time variability for both PwCI and HC's. There was no significant difference across groups, type of stimuli nor their interactions.

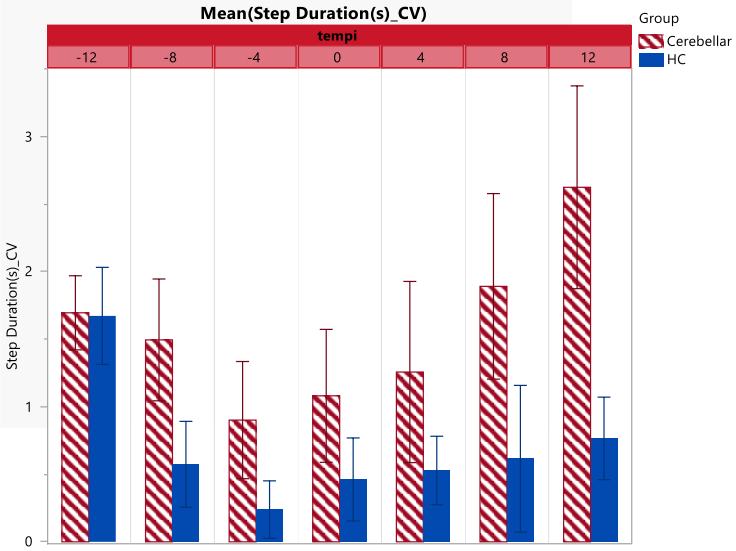

Figure 18: Step time variability (CV) - difference (condition-baseline)

Stride length (m): In figure 19 we see that the stride length of PwCI shortens when trying to synchronize to the auditory stimuli at various tempi compared to the baseline. HC's tend to lengthen their step when walking to the conditions, especially at higher tempi. The mixed model showed no significant effect tempi (P= 0.0917), but multiple comparisons showed a difference (P= 0.0302) between tempo -12 and +8% for both groups together. The interaction between group and tempi was almost significant (P= 0.0777). No effect of stimuli or other interactions effects were present.

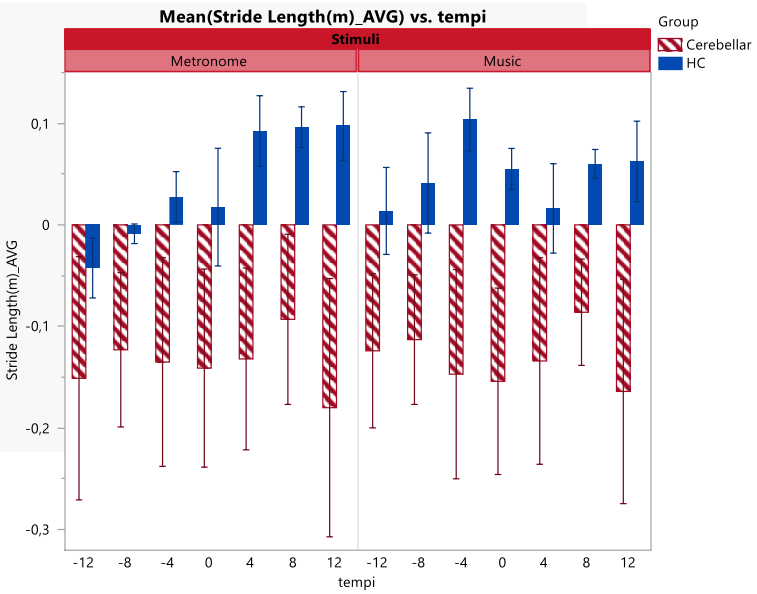

Figure 19: Stride length (m) - difference (condition-baseline)

Stride length variability (CV): In accordance with step time variability, the stride length variability was higher when walking to the conditions than the baseline walking measurement in PwCI (see figure 20). In HC's this was less the case, although no significant difference of stride length variability was found between groups (P= 0.1918). In figure 20 the step length variability tends to be slightly higher in metronomes than in music in PwCI and slightly lower in metronomes than in music in HC's. But the interaction group*stimuli was only significant with the overall test (P= 0.0346) and not when corrected for multiple comparisons by the post-hoc Tukey test.

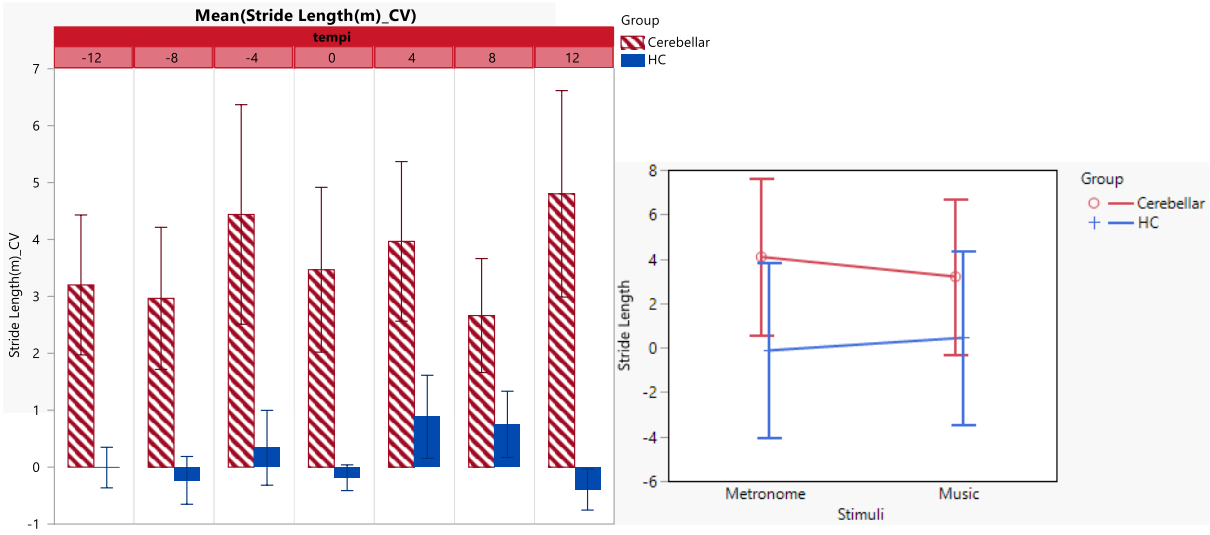

Figure 20: Stride length variability (CV) - difference (condition-baseline)

4.6 REPORTING ON INDIVIDUAL CASES

In the section below, the diagnosis and lesion location of each PwCI will be presented next to the clinical presentation and the most relevant motor, cognitive and affective descriptive test. The presence of one or more cerebellar syndrome will be discussed. The primary outcome measure of synchronization (Resultant of Vector Length) is reported separately for each PwCI at tempi 0%, +4% and -4% in Table 6.

Table 6: PwCI Resultant of vector length (RVL) for finger-tapping and walking at 4, 0 and -4%

Finger-tapping						
	Metronome			Music		
Participant	4%	0%	-4%	4%	0%	-4%
1	0,829	0,827	0,8212	0,711	0,793	0,717
2	0,952	0,949	0,975	0,793	0,941	0,412
3	0,831	0,78	0,855	0,882	0,903	0,864
4	0,734	0,61	0,819	*	*	*
5	0,75	0,96	0,85	0,757	0,858	0,85
Walking						
	Metronome			Music		
Participant	4%	0%	-4%	4%	0%	-4%
1	0,938	0,941	0,948	0,934	*	0,919
2	0,323	0,576	0,782	0,235	0,391	0,856
3	0,472	0,199	0,326	0,41	0,272	0,326
4	0,21	0,525	0,279	0,122	0,058	0,455
5	0,957	0,944	0,916	0,65	0,894	0,716

* missing data

Participant 1:

Diagnosis and MRI: A lesion in the left middle cerebellar peduncle for which the etiology was inconclusive. With symptoms of nystagmus and vertigo, a vestibular cerebellar syndrome could be suspected (Cabaraux et al., 2021). Although the lesion was not located in the cerebellum itself, it could block the pathways between the cerebellum and the vestibular and oculomotor nuclei in the pons and in this way explain her nystagmus and vertigo.

Motor and cognitive-affective testing: This participant scored good on all motor and cognitive tests. The baseline walking parameters seamed similar to those of health controls.

Synchronization measures: The participant had a good synchronization ability in the tapping and in the walking experiment according to the RVL (see Table 6).

Participant 2:

Diagnosis and MRI: A left posterior cerebellar stroke (Superior cerebellar artery territory). This artery irrigates the anterior lobe, part of lobule VI (where the sensorimotor cerebellar information is located) and the superior portion of the dentate nucleus. Lesions in this area typically reflect in a cerebellar motor syndrome: problems with coordination of gait, limb movement and speech (Cabaraux et al., 2021).

Motor testing: The scores on the SARA were relatively good with slight problems (score 1/8) in the 'gait' subscale and slight problems in upper limb coordination (score 0.5/4). The scores on the DGI and the NHPT were good, as well as the TUG with the best time (7 seconds) out of all PwCI.

Cognitive-affective testing: Cognitive symptoms were reported and confirmed by the CCAS/SS scale with 1 failed test meaning a possible diagnosis of CCAS/SS according to Hoche et al. (2018). This matches the MRI lesion location since the posterior lobe of the cerebellum plays a crucial role in the regulation of cognitive operations and emotions (Cabaraux et al., 2021). The participant scored way above the cut off score for anxiety and depression on the HADS. Important acknowledge is the additional left frontal anterior lesion. This extracerebellar lesion could also could also be the cause of the cognitive symptoms.

Synchronization measures: The synchronization ability was good in the tapping experiment while it was markedly lower in the walking experiment for the RVL (see Table 6).

Participant 3:

Diagnosis and MRI: Global cerebellar atrophy predominantly in the cerebellar vermis. The latter has been linked to the spinocerebellum and its function in the control of actual execution of movement by "comparing feedback from the spinal cord with the intended motor command", regulation of muscle tone and "feedforward mechanisms to regulate movement" (Shumway-Cook, A., & Woollacott, M. H., 2017, p. 72).

Motor testing: He had the worst score on motor testing's (TUG, SARA, DGI and NHPT left) out of all PwCI. In the SARA, the 'gait', 'stance' and the 'speech' subscales showed deficits (scores of 3/8, 2/6 and 2/6 respectively) and the upper limb ataxia test a score of 1/4 was reported with the 'Nose-finger test', 'Fast alternating hand movements' and the 'Heel-shin

slide'. With the symptoms of gait ataxia, steady state balance problems, dysarthria, dysmetria and dysdiadochokinesis this case is a clear example of a pure cerebellar motor syndrome, although vestibular and oculomotor deficits were not measured with our descriptive test battery so a vestibulo-cerebellar syndrome cannot be ruled out completely.

Cognitive-affective testing: No cognitive or affective symptoms were detected with the CCAS/SS scale. The cut off score for anxiety and depression were both met in de HADS questionnaire.

Synchronization measures: The synchronization ability was relatively good in the tapping experiment while in the walking experiment it was very low (see Table 6).

Participant 4:

Diagnosis and MRI: Spastic paraplegia type 7 and mutations in the CACNA1A gene. A consequence of this mutation is the dysfunction in voltage-gated calcium channels, which manifest a disorder called 'episodic ataxia type 2' with attacks of imbalance, vertigo, and ataxia (Strupp, Zwergal, & Brandt, 2007).

Motor testing: The subscales of the SARA showed mild gait (score 2/8), speech (score 1/6) and some upper limb coordination deficits in the subscales 'fast alternating hand movement' (score 1/4) and 'heel-shin slide' (score 1.5/4). The DGI showed slight problems with dynamic gait when head turning was involved and when she had to step over and around obstacles. Her manual dexterity measured by the NHPT was clearly above her predicted value for age and gender.

Cognitive-affective testing: The participant had the worst score on the CCAS/SS scale out of all PwCI with most problems in semantic and phonemic fluency, verbal recall and affect. The participant crossed the cut off score for depression in the HADS.

Synchronization measures: The synchronization ability was good in the tapping experiment and the lowest of all PwCI in the walking experiment (see Table 6), especially with music at higher tempi.

Participant 5:

Diagnosis and MRI: Right posterior paravermis (posterior inferior cerebellar artery) stroke.

Motor testing: Postural instability was reported by the participant, although the DGI revealed no dynamic gait deficits (score 24/24) and the SARA score was only 1/8 and 1/6 for the subscales 'gait' and 'stance' respectively.

Cognitive-affective testing: Although no cognitive deficits were not reported, lobule VI and VII of the posterior cerebellum are known to be connected with areas of the cerebral cortex via different cerebro-cerebellar loops, regulating cognitive and affective functions (Timmann& Daum, 2007); (Grimaldi& Manto, 2012); (Cabaraux et al., 2021). When tested with the CCAS/SS scale this participants had a score of 91/120 and failed on two tests, suggesting a probable diagnosis of CCAS/SS according to Hoche et al. (2018). The HADS showed some depression and anxiety but this did not cross the cut off score.

Synchronization measures: The synchronization ability was good in the tapping and in the walking and the experiment (see Table 6).

5 DISCUSSION

Amongst the PwCI included, the etiology and spatial distribution of the cerebellar lesion was different for each patient, which resulted in differences in clinical presentation. Participant number 201 experienced balance problems due to cerebellar vertigo and dizziness (predominantly the vestibular cerebellar syndrome) and had no ataxia according to the SARA score (0/40) and no dynamic gait deficit according to the DGI (24/24). In contrast, three participants who explicitly had ataxia (=having a higher score on the SARA especially for gait) might experience their balance and gait problems due to their motor incoordination (predominant cerebellar motor syndrome). This difference in underlying mechanism causing balance problems (motor incoordination vs. vertigo) is an important distinction to make. Vestibular and oculomotor deficits (vestibular cerebellar syndrome) present in isolation may benefit from other treatment strategies than proposed in this study. Therefore, the assessment of these cerebellar syndromes with sensitive scales is a crucial part of the process when investigating rehabilitation for PwCI.

Cerebellar ataxia scores measured by the SARA scale were relatively good in all PwCI, with the most deficits in the 'gait' subscale and some deficits in the 'fast alternating hand movements' subscale. Lesions for these dysfunctions would be expected in the anterior lobe, part of lobule VI and the superior portion of the dentate nucleus (Cabaraux et al., 2021). Dysdiadochokinesis especially has found to be linked to the dentate nucleus in a study on monkeys (Conrad& Brooks, 1974). For three out of four patients with a cerebellar motor syndrome, the MRI lesion (partly) included these regions.

PwCI and HC's were both able to synchronize with the beat in the tapping experiment. Still, as fundamental research of Nozaradan et al. (2017) suggested, it was less accurate in PwCI compared to HC's. Schwartze, Keller, and Kotz (2016) confirmed this in a previous finger tapping experiment with HC's and cerebellar patients, where the latter had a higher variability and worse synchronization ability during different tapping tasks. In our experiment, tapping at higher (or lower) rhythms did not change the synchronization outcomes in PwCI. This is contrast with the findings of Nozaradan et al. (2017) who analyzed neural tracking of rhythm on EEG. They suggest that the perceptual component of detecting

rhythms is less consistent at higher tempi. However, in our walking experiment, the influence of tempi was very clear in PwCI (not in HC's). Synchronization seemed to be higher at -8 and -4% in PwCI. This could be due to the different motor skills required for a tapping versus a walking task. While tapping is a seated and unilateral task, walking demands whole body coordination of the limbs and the control of body center of gravity within the base of support.

In both tapping and walking experiments, auditory-motor coupling was better with metronomes, which is in accordance with the results of Moumdjian et al. (2019) where HC's and persons with multiple sclerosis (PwMS) had better synchronization level with metronomes than with music.

The synchronization abilities of three out of five PwCI strongly decreased in the walking experiment compared to the tapping experiment, although they did not in HC's. This could be explained by the deficits in gait and balance due to cerebellar ataxia in PwCI. For example, participant number 3 which had the lowest synchronization ability of all participants showed also the worst scores on the SARA and the DGI, while participant number 1 had no ataxia and dynamic gait problems (max score on both SARA and DGI) and was able to synchronize as good as the HC's in the walking experiment. Another explanation for the better synchronization abilities in the tapping experiment than the walking experiment could be that the PwCI had very mild upper limb ataxia according to the subscales of the SARA. The most problems were observed in the 'fast alternating movements' subscale and the 'finger to nose test'. These symptoms of dysdiadochokinesis and dysmetria might not be that hindering to a tapping task were participants tap in a repetitive manner on a clear target. However, the manual dexterity measured with the NHPT was seen to be worse for participant 3 and 4, which also showed the worse synchronization measures in the tapping experiment.
These examples suggest that the motor ability of a PwCI during that specific motor task influences the auditory-motor coupling or synchronization ability. To confirm this, a factor analysis with these motor measurements should be conducted in a bigger cohort of PwCI.

An important reflection to make is the following: is the synchronization ability a requirement in order to have positive effects on the gait pattern in PwCI?

Baseline gait parameters were shown to be different across groups for speed, speed variability, double limb support, step time variability and stride length. These results are in accordance with the systematic review of Buckley, Mazzà, and McNeill (2018) on gait characteristics associated with cerebellar ataxia, were strong evidence was found that PwCI walked at lower speed, with an increased double limb support, an increased step time variability, and a decreased stride length amongst other parameters.

The cadence increased with the higher tempi and decreased with lower tempi for both groups compared to baseline, although in PwCI this directly proportional line was less linear in PwCI than in HC's. This trend was previously described in the study of Moumdjian et al. (2019) on PwMS, where a more linear increase in cadence according to the tempi was seen in HC's compared to PwMS when walking to metronomes at tempi (0%, +2%, +4%, +6%, +8% and +10%). Our preliminary results also showed (non-significant, graphical) that the cadence was more linear in HC's with metronomes compared to music. This could be due to the better synchronization in metronomes compared to music and a better synchronization in HC's compared to PwCI.

For gait speed and stride length, the same trend was seen: the speed and stride length of healthy controls seem to follow the tempi in a linear way (higher then baseline at higher tempi, lower then baseline at lower tempi). However, in PwCI the gait speed and stride length did not increase when walking to auditory stimuli, even at higher tempi. This is in contrast with patients with chronic stroke (n=41) in a study of Cha, Kim, and Chung (2014), who were able to increase their gait velocity when walking to +10% and +20% of their baseline walking measurement. However, their gait symmetry decreased at higher tempi compared to the baseline walking measurement, which suggests that the quality of their gait pattern decreased. The aim in PwCI may not be to increase the walking speed, but rather to improve the quality of their gait pattern. This was for example done in a case of Friedreich ataxia (14 year old female), where her wheeled walker was replaced by a U-step walking

stabilizer which lowered her gait speed for 42.9%. This decreased her rate of falls from 10 to 3 per month. (Harris-Love, Siegel, Paul, & Benson, 2004).

The history of falls is has been linked to temporal gait variability in persons with cerebellar ataxia (Schniepp et al., 2014) Therefor, this parameter should be the outcome of focus. Step time variability seemed to be slightly higher when walking to the auditory stimuli at all different tempi compared to the baseline, for both PwCI and HC's (not significant). This suggest that our experiment is challenging the participants to adapt their step time to the beat, and that we are actually training this parameter. Regardless of the group or stimuli provided, step time variability was lower at -4% compared to walking at -12% or +12% of the PWC. The lowest step time variability was observed at -4% and the -8% for the PwCI. As the PwCI showed also to best synchronize to the -8% and especially the -4% tempi, the latter could be their ideal tempi for training the step time variability in gait rehabilitation.

The spatial gait variability seems to be a less relevant indicator of risk of falls compared to the temporal gait variability (Schniepp et al., 2014). In this walking experiment the stride length variability did not differ across groups, stimuli or tempi, but in the PwCI it seemed to be higher when walking to auditory stimuli than the baseline measurement. In contrast, the mean lateral step variability tended to decrease in PwCI when walking to metronomes and music at all tempi compared to baseline (not in HC's). The lateral step variability has been linked to falls and tend to be higher in older adults (Skiadopoulos, Moore, Sayles, Schmid, & Stergiou, 2020); (Hausdorff, 2005). Although differences in this preliminary study were very small, this is worthy to further investigate with a bigger cohort of participants.

In this experiment, persons were instructed to synchronize to the beat. In a study of Baram and Miller (2007) on persons with multiple sclerosis and cerebellar ataxia, patients walked to rhythmic auditory stimuli that were adapting to the pace of their own steps. They showed an improvement in walking speed and stride length. This way of non-intended adaptive auditory-motor coupling could as well be further investigated in PwCI.

Limitations of this study are the risk of bias due to non-probability sampling methods, which lowers the generalizability of these results. Furthermore, a bigger sample needs to be investigated in order to generalize any of these results to the broader populations of PwCI. Still, as the clinical presentation of cerebellar impairments can be highly variable between individuals, a personalized approach in combination with other therapy modalities should always stay recommended.

Secondly, in this experiment participants walked in blocks of three minutes to the auditory stimuli, which is not enough to see gait training effects on the long term. A longer walking time could possibly reveal a learning effect by analyzing the synchronization and gait parameters minute per minute. Future intervention studies could investigate if these possible training effect with auditory stimuli would transfer to a better walking performance without auditory stimuli.

Lastly, current primary and secondary outcome measures used in this study do not reflect the impact on the daily life of PwCI. Although the history of falls has been linked to temporal gait variability (Schniepp et al., 2014) and the SARA has been correlated with the toe-out variability and the double-limb support time variability (Shah et al., 2021) in cerebellar ataxia, the link between improvement of gait parameters and meaningful changes in mobility or quality of life still remains unclear. Future intervention studies in this field should broaden up their outcome measures from function level (synchronization and spatiotemporal gait parameters) to measures on activity and participation level, such as the 6-minute walking test and the Box and Blocks test who have recently been linked to the walking independence in persons with hereditary ataxia's (Giangiardi et al., 2022) Further, the Patient-Reported Outcome measure of Ataxia has been developed, which captures 3 domains: physical, activities of daily living and mental health. The scale was shown to be valid and reliable in 147 patients with cerebellar ataxia (Schmahmann, Pierce, MacMore, & L'Italien, 2021). These outcome measures could be used in order to have more holistic view on the true impact of our interventions.

6 CONCLUSION

These preliminary results indicate that the synchronisation abilities of PwCI are higher when finger tapping than when walking to rhythmic auditory stimuli. Different mechanisms of action may be present between these tasks. Further investigation in a bigger sample is needed to understand the auditory-motor coupling during walking in PwCI. Even in this small cohort of participants, gait parameters showed differences across tempi, group and stimuli. The preliminary results support the hypothesis that walking to music and metronomes at tempi lower (-4%) than their preferred walking cadence could benefit the walking pattern in terms of temporal gait variability. On the long term, an intervention study on gait training with rhythmic auditory stimuli should be conducted, in order to investigate the benefits not only on gait pattern, but also on activity and participation in PwCI.

7 TABLE LIST

8 FIGURE LIST

9 REFERENCE LIST

Uncategorized References

Baer, L. H., Park, M. T., Bailey, J. A., Chakravarty, M. M., Li, K. Z., & Penhune, V. B. (2015). Regional cerebellar volumes are related to early musical training and finger tapping performance. *Neuroimage, 109*, 130-139. doi:10.1016/j.neuroimage.2014.12.076

Baram, Y., & Miller, A. (2007). Auditory feedback control for improvement of gait in patients with Multiple Sclerosis. *J Neurol Sci, 254*(1-2), 90-94. doi:10.1016/j.jns.2007.01.003

Barbuto, S., Mackenzie, S., Kuo, S. H., Kitago, T., & Stein, J. (2020). Measurements of Hand Function in Degenerative Cerebellar Disease: A Case-Control Pilot Study. *Am J Phys Med Rehabil, 99*(9), 795-800. doi:10.1097/phm.0000000000001411

Beekman, E., Mesters, I., Gosselink, R., Klaassen, M. P., Hendriks, E. J., Van Schayck, O. C., & de Bie, R. A. (2014). The first reference equations for the 6-minute walk distance over a 10 m course. *Thorax, 69*(9), 867-868. doi:10.1136/thoraxjnl-2014-205228

Buckley, E., Mazzà, C., & McNeill, A. (2018). A systematic review of the gait characteristics associated with Cerebellar Ataxia. *Gait Posture, 60*, 154-163. doi:10.1016/j.gaitpost.2017.11.024

Buhmann, J., Desmet, F., Moens, B., Van Dyck, E., & Leman, M. (2016). Spontaneous Velocity Effect of Musical Expression on Self-Paced Walking. *PLoS One, 11*(5), e0154414. doi:10.1371/journal.pone.0154414

Buhmann, J., & Masson, J. (2016). *Cochen De Cock, V., Damm, L., and Leman, M.(2016b). "Music selection: a user-and task specific protocol,".* Paper presented at the Motor Behaviour and Emotion; International Congress.

Cabaraux, P., Gandini, J., & Manto, M. (2021, 2021//). *The Three Cornerstones of Cerebellar Ataxia: Closing the Loop of 200 Years of Cerebellar Research.* Paper presented at the Cerebellum as a CNS Hub, Cham.

Caplan, B., & Mendoza, J. E. (2011). Edinburgh Handedness Inventory. In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology* (pp. 928-928). New York, NY: Springer New York.

Cha, Y., Kim, Y., & Chung, Y. (2014). Immediate effects of rhythmic auditory stimulation with tempo changes on gait in stroke patients. *Journal of physical therapy science, 26*(4), 479-482. doi:10.1589/jpts.26.479

Conrad, B., & Brooks, V. B. (1974). Effects of dentate cooling on rapid alternating arm movements. *J Neurophysiol, 37*(4), 792-804. doi:10.1152/jn.1974.37.4.792

Crosby, L. D., Chen, J. L., Grahn, J. A., & Patterson, K. K. (2022). The Effect of Rhythm Abilities on Metronome-Cued Walking with an Induced Temporal Gait Asymmetry in Neurotypical Adults. *J Mot Behav, 54*(3), 267-280. doi:10.1080/00222895.2021.1953959

Debouverie, M., Pittion-Vouyovitch, S., Louis, S., & Guillemin, F. (2007). Validity of a French version of the fatigue impact scale in multiple sclerosis. *Mult Scler, 13*(8), 1026-1032. doi:10.1177/1352458507077942

Fonteyn, E. M., Keus, S. H., Verstappen, C. C., Schöls, L., de Groot, I. J., & van de Warrenburg, B. P. (2014). The effectiveness of allied health care in patients with ataxia: a systematic review. *J Neurol, 261*(2), 251-258. doi:10.1007/s00415-013-6910-6

Forte, R., Tocci, N., & De Vito, G. (2021). The Impact of Exercise Intervention with Rhythmic Auditory Stimulation to Improve Gait and Mobility in Parkinson Disease: An Umbrella Review. *Brain Sci, 11*(6). doi:10.3390/brainsci11060685

Giangiardi, V. F., Perracini, M. R., da Silva, M. L., Setti, G. B. R., Curzio, L. E., Vegas, M., & Alouche, S. R. (2022). Functional Outcomes Associated With Independence in Walking Among People With Hereditary Ataxias: An Exploratory Cross-sectional Study. *Phys Ther, 102*(4). doi:10.1093/ptj/pzac006

Grimaldi, G., & Manto, M. (2012). Topography of cerebellar deficits in humans. *Cerebellum, 11*(2), 336-351. doi:10.1007/s12311-011-0247-4

Harris-Love, M. O., Siegel, K. L., Paul, S. M., & Benson, K. (2004). Rehabilitation management of Friedreich ataxia: lower extremity force-control variability and gait performance. *Neurorehabil Neural Repair, 18*(2), 117-124. doi:10.1177/0888439004267241

Hausdorff, J. M. (2005). Gait variability: methods, modeling and meaning. *J Neuroeng Rehabil, 2*, 19. doi:10.1186/1743-0003-2-19

He, M., Zhang, H. N., Tang, Z. C., & Gao, S. G. (2021). Balance and coordination training for patients with genetic degenerative ataxia: a systematic review. *J Neurol, 268*(10), 3690-3705. doi:10.1007/s00415-020-09938-6

Hoche, F., Guell, X., Vangel, M. G., Sherman, J. C., & Schmahmann, J. D. (2018). The cerebellar cognitive affective/Schmahmann syndrome scale. *Brain, 141*(1), 248-270. doi:10.1093/brain/awx317

Ilg, W., & Timmann, D. (2013). Gait ataxia--specific cerebellar influences and their rehabilitation. *Mov Disord, 28*(11), 1566-1575. doi:10.1002/mds.25558

Lin, C., Arevalo, Y. A., Harvey, R. L., Prabhakaran, S., & Martin, K. D. (2022). The minimal clinically important difference of the motricity index score. *Top Stroke Rehabil*, 1-6. doi:10.1080/10749357.2022.2031532

Marquer, A., Barbieri, G., & Pérennou, D. (2014). The assessment and treatment of postural disorders in cerebellar ataxia: a systematic review. *Ann Phys Rehabil Med, 57*(2), 67-78. doi:10.1016/j.rehab.2014.01.002

Marsden, J. F. (2018a). Cerebellar ataxia. In B. L. Day & S. R. Lord (Eds.), *Balance, Gait, and Falls* (Vol. 159, pp. 261-281).

Marsden, J. F. (2018b). Cerebellar ataxia. *Handb Clin Neurol, 159*, 261-281. doi:10.1016/b978-0-444-63916-5.00017-3

Marsden, J. F. (2018c). Cerebellar ataxia. *Handb Clin Neurol, 159*, 261. doi:10.1016/b978-0-444-63916-5.00017-3

Matsugi, A. (2017). Physical Therapy for Cerebellar Ataxia. In.

Meseguer-Henarejos, A. B., Sánchez-Meca, J., López-Pina, J. A., & Carles-Hernández, R. (2018). Inter- and intra-rater reliability of the Modified Ashworth Scale: a systematic review and meta-analysis. *Eur J Phys Rehabil Med, 54*(4), 576-590. doi:10.23736/s1973-9087.17.04796-7

Mills, R. J., Young, C. A., Pallant, J. F., & Tennant, A. (2010). Rasch analysis of the Modified Fatigue Impact Scale (MFIS) in multiple sclerosis. *J Neurol Neurosurg Psychiatry, 81*(9), 1049-1051. doi:10.1136/jnnp.2008.151340

Moens, B., Muller, C., van Noorden, L., Franěk, M., Celie, B., Boone, J., . . . Leman, M. (2014). Encouraging spontaneous synchronisation with D-Jogger, an adaptive music player that aligns movement and music. *PLoS One, 9*(12), e114234. doi:10.1371/journal.pone.0114234

Morton, S. M., & Bastian, A. J. (2004). Cerebellar control of balance and locomotion. *Neuroscientist, 10*(3), 247-259. doi:10.1177/1073858404263517

Moumdjian, L., Buhmann, J., Willems, I., Feys, P., & Leman, M. (2018). Entrainment and Synchronization to Auditory Stimuli During Walking in Healthy and Neurological Populations: A Methodological Systematic Review. *Front Hum Neurosci, 12*, 263. doi:10.3389/fnhum.2018.00263

Moumdjian, L., Moens, B., Maes, P. J., Van Nieuwenhoven, J., Van Wijmeersch, B., Leman, M., & Feys, P. (2019). Walking to Music and Metronome at Various Tempi in Persons With Multiple Sclerosis: A Basis for Rehabilitation. *Neurorehabil Neural Repair, 33*(6), 464-475. doi:10.1177/1545968319847962

Moumdjian, L., Rosso, M., Moens, B., De Weerdt, N., Leman, M., & Feys, P. (2022). A case-study of a person with multiple sclerosis and cerebellar ataxia synchronizing finger-taps and foot-steps to music and metronomes. *Neuroimmunology Reports, 2*, 100101. doi:https://doi.org/10.1016/j.nerep.2022.100101

Nozaradan, S., Schwartze, M., Obermeier, C., & Kotz, S. A. (2017). Specific contributions of basal ganglia and cerebellum to the neural tracking of rhythm. *Cortex, 95*, 156-168. doi:10.1016/j.cortex.2017.08.015

Oxford Grice, K., Vogel, K. A., Le, V., Mitchell, A., Muniz, S., & Vollmer, M. A. (2003). Adult norms for a commercially available Nine Hole Peg Test for finger dexterity. *Am J Occup Ther, 57*(5), 570-573. doi:10.5014/ajot.57.5.570

Peretz, I., Champod, A., & Hyde, K. (2003). Varieties of Musical Disorders: The Montreal Battery of Evaluation of Amusia. *Annals of the New York Academy of Sciences, 999*, 58-75. doi:10.1196/annals.1284.006

Philipp, B. (2009). CircStat: a MATLAB toolbox for circular statistics. *Journal of Statistical Software, 31*. doi:10.18637/jss.v031.i10

Pilotto, F., & Saxena, S. (2018). Epidemiology of inherited cerebellar ataxias and challenges in clinical research. *Clinical and Translational Neuroscience, 2*, 2514183X1878525. doi:10.1177/2514183X18785258

Podsiadlo, D., & Richardson, S. (1991). The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc, 39*(2), 142-148. doi:10.1111/j.1532-5415.1991.tb01616.x

Powell, L. E., & Myers, A. M. (1995). The Activities-specific Balance Confidence (ABC) Scale. *J Gerontol A Biol Sci Med Sci, 50a*(1), M28-34. doi:10.1093/gerona/50a.1.m28

Reoli, R., Therrien, A., Cherry-Allen, K., Keller, J., Millar, J., & Bastian, A. (2021). Is the dynamic gait index a useful outcome to measure balance and ambulation in patients with cerebellar ataxia? *Gait Posture, 89*, 200-205. doi:10.1016/j.gaitpost.2021.07.011

Richard L. Harvey, M., Richard F. Macko, MD, Joel Stein, MD, Carolee J. Winstein, PhD, PT, FAPTA, Richard D. Zorowitz, MD. (2008). *Stroke Recovery and Rehabilitation*: MD

Demos Medical Publishing.

Roberge, P., Doré, I., Menear, M., Chartrand, E., Ciampi, A., Duhoux, A., & Fournier, L. (2013). A psychometric evaluation of the French Canadian version of the Hospital Anxiety and Depression Scale in a large primary care population. *J Affect Disord, 147*(1-3), 171-179. doi:10.1016/j.jad.2012.10.029

Rosso, M., Leman, M., & Moumdjian, L. (2021). Neural Entrainment Meets Behavior: The Stability Index as a Neural Outcome Measure of Auditory-Motor Coupling. *Front Hum Neurosci, 15*, 668918. doi:10.3389/fnhum.2021.668918

Salbach, N. M., Mayo, N. E., Hanley, J. A., Richards, C. L., & Wood-Dauphinee, S. (2006). Psychometric evaluation of the original and Canadian French version of the activities-specific balance confidence scale among people with stroke. *Arch Phys Med Rehabil, 87*(12), 1597-1604. doi:10.1016/j.apmr.2006.08.336

Schmahmann, J. D., Pierce, S., MacMore, J., & L'Italien, G. J. (2021). Development and Validation of a Patient-Reported Outcome Measure of Ataxia. *Mov Disord, 36*(10), 2367-2377. doi:10.1002/mds.28670

Schmahmann, J. D., & Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain, 121 (Pt 4)*, 561-579. doi:10.1093/brain/121.4.561

Schmitz-Hübsch, T., du Montcel, S. T., Baliko, L., Berciano, J., Boesch, S., Depondt, C., . . . Fancellu, R. (2006). Scale for the assessment and rating of ataxia: development of a new clinical scale. *Neurology, 66*(11), 1717-1720. doi:10.1212/01.wnl.0000219042.60538.92

Schniepp, R., Wuehr, M., Schlick, C., Huth, S., Pradhan, C., Dieterich, M., . . . Jahn, K. (2014). Increased gait variability is associated with the history of falls in patients with cerebellar ataxia. *J Neurol, 261*(1), 213-223. doi:10.1007/s00415-013-7189-3

Schwartze, M., Keller, P. E., & Kotz, S. A. (2016). Spontaneous, synchronized, and corrective timing behavior in cerebellar lesion patients. *Behavioural Brain Research, 312*, 285-293. doi:10.1016/j.bbr.2016.06.040

Shah, V. V., Rodriguez-Labrada, R., Horak, F. B., McNames, J., Casey, H., Hansson Floyd, K., . . . Gomez, C. M. (2021). Gait Variability in Spinocerebellar Ataxia Assessed Using Wearable Inertial Sensors. *Mov Disord, 36*(12), 2922-2931. doi:10.1002/mds.28740

Shumway-Cook, A., & Woollacott, M. H. (1995). *Motor control : theory and practical applications*: Baltimore (Md.) : Williams and Wilkins.

Skiadopoulos, A., Moore, E. E., Sayles, H. R., Schmid, K. K., & Stergiou, N. (2020). Step width variability as a discriminator of age-related gait changes. *J Neuroeng Rehabil, 17*(1), 41. doi:10.1186/s12984-020-00671-9

Stolze, H., Klebe, S., Petersen, G., Raethjen, J., Wenzelburger, R., Witt, K., & Deuschl, G. (2002). Typical features of cerebellar ataxic gait. *J Neurol Neurosurg Psychiatry, 73*(3), 310-312. doi:10.1136/jnnp.73.3.310

Strupp, M., Zwergal, A., & Brandt, T. (2007). Episodic ataxia type 2. *Neurotherapeutics, 4*(2), 267-273. doi:10.1016/j.nurt.2007.01.014

Timmann, D., & Daum, I. (2007). Cerebellar contributions to cognitive functions: a progress report after two decades of research. *Cerebellum, 6*(3), 159-162. doi:10.1080/14734220701496448

Washabaugh, E. P., Kalyanaraman, T., Adamczyk, P. G., Claflin, E. S., & Krishnan, C. (2017). Validity and repeatability of inertial measurement units for measuring gait parameters. *Gait Posture, 55*, 87-93. doi:10.1016/j.gaitpost.2017.04.013

Weyer, A., Abele, M., Schmitz-Hübsch, T., Schoch, B., Frings, M., Timmann, D., & Klockgether, T. (2007). Reliability and validity of the scale for the assessment and rating of ataxia: a study in 64 ataxia patients. *Mov Disord, 22*(11), 1633-1637. doi:10.1002/mds.21544

Willems, A. M., Nieuwboer, A., Chavret, F., Desloovere, K., Dom, R., Rochester, L., . . . Van Wegen, E. (2006). The use of rhythmic auditory cues to influence gait in patients with Parkinson's disease, the differential effect for freezers and non-freezers, an explorative study. *Disabil Rehabil, 28*(11), 721-728. doi:10.1080/09638280500386569

Winser, S., Smith, C. M., Hale, L. A., Claydon, L. S., Whitney, S. L., Klatt, B., . . . Heyman, R. (2017). Psychometric Properties of a Core Set of Measures of Balance for People With Cerebellar Ataxia Secondary to Multiple Sclerosis. *Arch Phys Med Rehabil, 98*(2), 270-276. doi:10.1016/j.apmr.2016.07.023

Winser, S. J., Smith, C., Hale, L. A., Claydon, L. S., & Whitney, S. L. (2015). Balance outcome measures in cerebellar ataxia: a Delphi survey. *Disabil Rehabil, 37*(2), 165-170. doi:10.3109/09638288.2014.913709

Zhang, L., Cao, B., Ou, R., Wei, Q. Q., Zhao, B., Yang, J., . . . Shang, H. (2017). Non-motor symptoms and the quality of life in multiple system atrophy with different subtypes. *Parkinsonism Relat Disord, 35*, 63-68. doi:10.1016/j.parkreldis.2016.12.007

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatr Scand, 67*(6), 361-370. doi:10.1111/j.1600-0447.1983.tb09716.x

Books:

Shumway-Cook, A., & Woollacott, M. H. (2017). *Motor Control*. Wolters Kluwer.

Web pages:

A. (2019, 7 oktober). *Comprehensive Gait and Balance Analysis - APDM Wearable Technologies*. APDM. Geraadpleegd op 19 mei 2022, van https://apdm.com/mobility/

10 APPENDICES

1) Scale for the Assessment and Rating of Ataxia (SARA)
2) Approval ethical committee University of Hasselt
3) Progress from 'inventarisatieformulier'

Rater: _____date: _____patient:_____

Scale for the assessment and rating of ataxia (SARA)

1) Gait

Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.

0 Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed)
1 Slight difficulties, only visible when walking 10 consecutive steps in tandem
2 Clearly abnormal, tandem walking >10 steps not possible
3 Considerable staggering, difficulties in half-turn, but without support
4 Marked staggering, intermittent support of the wall required
5 Severe staggering, permanent support of one stick or light support by one arm required
6 Walking > 10 m only with strong support (two special sticks or stroller or accompanying person)
7 Walking < 10 m only with strong support (two special sticks or stroller or accompanying person)
8 Unable to walk, even supported

Score _____

2) Stance

Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated.

0 Normal, able to stand in tandem for > 10 s
1 Able to stand with feet together without sway, but not in tandem for > 10s
2 Able to stand with feet together for > 10 s, but only with sway
3 Able to stand for > 10 s without support in natural position, but not with feet together
4 Able to stand for >10 s in natural position only with intermittent support
5 Able to stand >10 s in natural position only with constant support of one arm
6 Unable to stand for >10 s even with constant support of one arm

Score _____

3) Sitting

Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.

0 Normal, no difficulties sitting >10 sec
1 Slight difficulties, intermittent sway
2 Constant sway, but able to sit > 10 s without support
3 Able to sit for > 10 s only with intermittent support
4 Unable to sit for >10 s without continuous support

Score _____

4) Speech disturbance

Speech is assessed during normal conversation.

0 Normal
1 Suggestion of speech disturbance
2 Impaired speech, but easy to understand
3 Occasional words difficult to understand
4 Many words difficult to understand
5 Only single words understandable
6 Speech unintelligible / anarthria

Score _____

Rater: _____date: _____patient:_____

5) Finger chase

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband´s reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.

- **0 No dysmetria**
- **1 Dysmetria, under/ overshooting target <5 cm**
- **2 Dysmetria, under/ overshooting target < 15 cm**
- **3 Dysmetria, under/ overshooting target > 15 cm**
- **4 Unable to perform 5 pointing movements**

Score	**R**ight	**L**eft
mean of both sides (R+L)/2		

6) Nose-finger test

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.

- **0 No tremor**
- **1 Tremor with an amplitude < 2 cm**
- **2 Tremor with an amplitude < 5 cm**
- **3 Tremor with an amplitude > 5 cm**
- **4 Unable to perform 5 pointing movements**

Score	**R**ight	**L**eft
mean of both sides (R+L)/2		

7) Fast alternating hand movements

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

- **0 Normal, no irregularities (performs <10s)**
- **1 Slightly irregular (performs <10s)**
- **2 Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10s**
- **3 Very irregular, single movements difficult to distinguish or relevant interruptions, performs >10s**
- **4 Unable to complete 10 cycles**

Score	**R**ight	**L**eft
mean of both sides (R+L)/2		

8) Heel-shin slide

Rated separately for each side
Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.

- **0 Normal**
- **1 Slightly abnormal, contact to shin maintained**
- **2 Clearly abnormal, goes off shin up to 3 times during 3 cycles**
- **3 Severely abnormal, goes off shin 4 or more times during 3 cycles**
- **4 Unable to perform the task**

Score	**R**ight	**L**eft
mean of both sides (R+L) / 2		

www.uhasselt.be
Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek
T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be

Definitief gunstig advies

Faculteit Geneeskunde en Levenswetenschappen
Comité voor Medische Ethiek
Voorzitter: prof. dr. Ivo Lambrichts
Secretariaat: Marleen Missotten
Tel.: 011 26 85 02
Fax: 011 26 85 99
E-mail: cme@uhasselt.be

ons kenmerk	uw kenmerk	Diepenbeek
CME2021/020		15/04/2021

Titel protocol	**Understanding the effect of variances on precision in predictive coding when walking to music and metronomes in persons with Cerebellar lesions.**
Nummer protocol	
Opdrachtgever	Universiteit Hasselt
Eudractnummer	
Belgisch nummer	**B1152021000003**
Onderzoeker	Prof. dr. Peter Feys, dr. Lousin Moumdjian

Geachte collega,

Op 16 februari 2021 werd het hierboven vernoemd dossier ingediend bij het CME UHasselt. Op 02 april 2021 werd een voorlopig advies opgemaakt.

Na inzage van de bijkomende informatie en/of aangepaste documenten met betrekking tot dit dossier is het Comité voor Medische Ethiek UHasselt van oordeel dat de voorgestelde studie, zoals beschreven in het protocol, wetenschappelijk relevant en ethisch verantwoord is.

Het definitief gunstig advies betreft de volgende documenten:
- Protocol versie 1., dd 16/02/2021
- Informatie en toestemmingsformulier versie 2.0, dd 05/04/2021
- Bewijs van 'No-fault' verzekering, dd 02/01/2021
- Vragenlijsten
- Flyer
- CV's en GCP attesten

Het Comité voor Medische Ethiek van UHasselt handelt volgens de geldende richtlijnen van de 'International Conference of Harmonization (ICH) Good Clinical Practice (GCP)' en volgens alle geldende en van toepassing zijnde wetten en reglementen.

Dit gunstig advies houdt niet in dat het Comité de verantwoordelijkheid voor de geplande studie op zich neemt. De onderzoeker blijft zelf verantwoordelijk hiervoor. Bovendien dient u erover te waken dat uw mening als betrokken onderzoeker wordt weergegeven in publicaties, rapporten voor de overheid enz., die het resultaat zijn van dit onderzoek.

Het comité vraagt aan de onderzoeker op de hoogte te worden gehouden wanneer de studie wordt gestart of wanneer ze wordt afgesloten of vroegtijdig onderbroken (met opgave van reden)

Indien de studie niet binnen het jaar beëindigd is dient de onderzoeker een jaarlijks rapport met het verloop van de studie te bezorgen aan het CME UHasselt.

www.uhasselt.be
Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek
T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be

Bij Serious Adverse events (SAE's) dient de onderzoeker het comité hiervan op de hoogte te brengen.

Wijzigingen in het studieprotocol, informatie en toestemmingsformulier, onderzoeksteam) dienen te worden goedgekeurd door het Comité via een amendement.

Wanneer een studie beëindigd wordt dient de onderzoeker een studierapport op te maken met het verloop van de studie (startdatum, einddatum, aantal geïncludeerde patiënten, aantal drop-outs, aantal patiënten die de studie volledig doorlopen hebben, eventuele adverse events, …

Met oprechte hoogachting,

Prof. dr. Ivo Lambrichts
Voorzitter Comité voor Medische Ethiek

Cc:

FAGG – Research & Development department, Victor Hortaplein 40, bus 40, 1060 Brussel
Comité d'Ethique Hôpital Civil Marie Curie, Chaussée de Bruxelles 140 à 6142 Lodelinsart

www.uhasselt.be
Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek
T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be

UHASSELT
KNOWLEDGE IN ACTION

INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
08/02/2022	- Introduction, discuss available data and study protocol - Share information for formulation RQ	Promotor: Copromotor/Begeleider: Lousin Moumdjian Student(e): Anne Student(e):
08/04/2022	- Discuss proposed RQ - Info about methodology - Pre-processing data - Data management and analysis/statistics	Promotor: Copromotor/Begeleider: Lousin Moumdjian Student(e): Anne Student(e):
26/04/2022	- Discuss results of preprocessing and data analysis	Promotor: Copromotor/Begeleider: Lousin Moumdjian Student(e): Anne Student(e):
04/05/2022	- Discuss methodology, participants demographics and descriptive testing	Promotor: Copromotor/Begeleider: Lousin Moumdjian Student(e): Anne Student(e):
05/05/2022	- Discuss final results	Promotor: Copromotor/Begeleider: Lousin Moumdjian Student(e): Anne Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):