

Persons with cerebral palsy display improved occipital cortical entrainment after gait training

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ABSTRACT

Prior neuroimaging work has shown that people with cerebral palsy (CP) often have visual processing impairments that impact their motor actions. We evaluated if a physical therapy gait training paradigm that incorporated visuomotor tasks has the potential to improve mobility and result in training-related changes in the entrainment of the occipital cortices of people with CP. People with CP (N = 29; Age = 19.9 ± 7.3 years; Gross Motor Classification Score Levels I-III) underwent 24 gait training sessions and completed a comprehensive battery of clinical assessments to quantify their mobility improvements. Magnetoencephalography (MEG) was used to image the cortical activity induced by viewing a 15 Hz flashing stimulus before and after therapy. Neurotypical controls (N = 34; Age = 23.1 ± 3.7 years) were used to gauge the extent of the cortical aberrations and the direction of treatment effects. The group with CP exhibited significantly weaker neural activity in the occipital cortices relative to the neurotypical controls prior to therapy. However, the strength of this event-related synchronization (ERS) increased following therapy. Furthermore, those with a larger change in the strength of the ERS tended to have the greatest improvements in preferred walking speed after therapy. Gait training paradigms that incorporate visuomotor tasks might have the potential to improve mobility, as well as occipital cortical activity in people with CP.

Introduction

Cerebral Palsy (CP) is a prevalent neurodevelopmental condition appearing intrauterine or shortly after birth, and is often due to a non-progressive insult to the developing brain (Bax et al., 2005). The number of children born with CP is currently on the rise worldwide due to advancements in the neonatal care of premature infants (DeMauro et al., 2024). Traditionally, CP is viewed heavily as a motor-centric condition, with core symptoms of altered mobility, coordination, posture and balance (Wood and Rosenbaum, 2000). Numerous structural neuroimaging studies have revealed that these motor impairments are partially due to disruptions in the thalamocortical and corticospinal white matter tracts (Staudt et al., 2003; Fowler et al., 2009; Vuong et al., 2023). Despite the motor-centric viewpoint, there is a growing recognition that 60 to 70 percent of youth with CP also have visual processing impairments that likely play a role in their visuomotor perceptions and the fidelity of their motor actions (Tinelli et al., 2020). Such visual

processing impairments are possibly due to the proximity of the optic radiations to the region where corticospinal tract damage often occurs (Schenk-Rootlieb et al., 1994; Ghate et al., 2016; Tinelli et al., 2020). Recent diffusion-weighted imaging has confirmed that disturbances in the optic radiations are often coupled to aberrations in the visuospatial attention of youth with CP (Araneda et al., 2022). Moreover, these disruptions are likely at least partially responsible for the reduced visual acuity and contrast sensitivity commonly reported in the clinical literature (Ozturk et al., 2013; Ickx et al., 2018; Tinelli et al., 2020). Overall, these emerging results point to the notion that many youth with CP might have a cortical vision impairment (Galli et al., 2022), but far less attention has been directed towards understanding the underlying neurophysiology of such impairments.

In a series of prior magnetoencephalographic (MEG) neuroimaging studies, we have shown that the spectrally specific cortical oscillations serving the components of visual processing and attention are altered in youth with CP. These investigations have demonstrated that people with

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CP have weaker cortical oscillations in the primary visual cortices (V1) during the performance of a visuomotor knee isometric force-matching task (Kurz et al., 2017; Busboom et al., 2022). These data further illustrate that there is a tight connection between altered visual processing and the motor actions of people with CP. We have also found fundamental differences in the visual activity of those with CP, including weaker oscillations in occipital cortices while viewing contrasting visual stimuli (VerMaas et al., 2020) and while attending to spatially distinct visual stimuli (VerMaas et al., 2021). Moreover, we have reported weaker cortical oscillations in people with CP in the V5/Visual MT area while viewing moving stimuli, implying that the visual processing deficits seen in persons with CP extend beyond the primary visual cortices (VerMaas et al., 2019a). The weaker cortical oscillations reported across these seminal studies may indicate less synchronous firing among pyramidal cells in the sensory cortices or possibly fewer neurons due to structural abnormalities/lesions in people with CP. Nevertheless, we contend that these altered vision-related cortical oscillations are central to the mobility deficits seen in those with CP (Sansare et al., 2022).

Currently, there is a lack of consensus on the optimal treatment paradigms that will improve mobility and no physical therapy investigations have directly targeted the visual processing of people with CP (Moreau et al., 2016; Novak et al., 2020). Many of the prior treatment trends have focused on improving muscular performance (i.e., strength training, power training) under the notion that it will have cascading effects on an individual's overall mobility and lower extremity motor control (Damiano et al., 2010; Moreau et al., 2013; Hoffman et al., 2017; Busboom et al., 2022; Hanssen et al., 2022). The findings from these investigations have been mixed, with some individuals demonstrating clinically relevant improvements and others showing few benefits. Previously, we completed a study aimed at evaluating potential changes in the cortical oscillations of people with CP following a lower extremity closed-chain power training protocol on the Total Gym system (Busboom et al., 2022). Although there were prominent improvements in the sensorimotor cortical oscillations and muscular function, there were no clinically relevant changes in the strength of oscillations in the visual cortices. Furthermore, the post-therapy improvements in gait were modest. These results are not completely surprising since practicing closed-chain fast motor actions doesn't directly involve the visuomotor integration associated with gait. Thus, we contend that a gait training approach that incorporates visuomotor activities may have more beneficial effects on the visual processing deficits seen in people with CP and ultimately also improve their mobility.

The purpose of this investigation was to evaluate if a physical therapy gait training paradigm that incorporates visuomotor tasks results in training-related changes in clinical motor outcomes and occipital cortical oscillations in people with CP. To that end, MEG neuroimaging was used to assess the strength of occipital cortical entrainment to a 15 Hz flickering visual stimulus before and after undergoing eight weeks (e.g., 24 sessions) of gait training. A visual entrainment paradigm was used because it provides a quantitative metric of the ability of occipital cortical neurons to match a visual stimulus and sustain the response throughout stimulation (Heinrichs-Graham and Wilson, 2012; Heinrichs-Graham et al., 2017; Wiesman and Wilson, 2019; Wiesman and Groff, 2019; Springer et al., 2022, 2023; Petro et al., 2024). In addition to the MEG assessments, a battery of clinical outcomes was collected to evaluate the degree of motor improvements seen after the gait training. We hypothesized that, compared with neurotypical controls, individuals with CP would display weaker entrainment of the occipital cortices before starting the gait training. We also hypothesized that after undergoing gait training, the individuals with CP would exhibit improvements in their overall mobility and occipital cortical entrainment. Lastly, we hypothesized that the respective mobility improvements would be correlated with changes in the strength of entrainment within the occipital cortices during stimulus processing.

Methods

The Boys Town National Research Hospital's Institutional Review Board reviewed and approved the protocol for this investigation. This investigation was also registered on clinicaltrials.gov (NCT05158218).

Participants

Sixty-three participants were included in this investigation. Twenty-nine of the participants had a diagnosis of CP (Age = 19.9 ± 7.3 years; Gross Motor Classification Score (GMFCS) levels I-III; Females = 14) and thirty-four were neurotypical controls (N = 34; Age = 23.1 ± 3.7 years; Females = 15). For the participants with CP, the exclusion criteria included any orthopedic surgery within the last 12 months, botulinum injections within the last six months, prior history of epilepsy or seizure activity, and any neurologic or psychiatric disorder not related to CP. None of the participants included in this investigation were undergoing concurrent gait related physical therapy during this study. For the neurotypical controls, the exclusion criteria were any prior orthopedic surgery or neurological or psychiatric disorder. For both groups, participants were also excluded if they had metal in their body that would prohibit an MRI or create an artifact in the collected MEG data that could not be removed with signal processing (e.g., braces on teeth). In addition, all the individuals had spastic CP with primarily white matter injuries and no large lesions (i.e., holes) that affect the cortical surface. Evaluation of the integrity of the cortical surface was determined via the professional neuroradiological read that accompanied the participant's MRI scan. Each participant and/or their parent/guardian provided written assent and consent, respectively, to participate in the investigation. The enrolled participants with CP had GMFCS between I and III. GMFCS levels range from I to V and are the most widely utilized clinical assessments for quantifying the extent of the mobility impairments seen in persons with CP for databases, clinical research, and program evaluation (Eliasson et al., 2007; Palisano et al., 2008). A participant with GMFCS level II has difficulty walking on uneven surfaces and has decreased walking speed, while a participant with GMFCS level III has difficulty walking longer distances and relies on mobility aides (i.e., forearm crutches, wheeled walker). The neurotypical controls included in this investigation did not undergo the gait training but underwent the MEG and clinical assessments. Their data was used to determine the extent of differences in cortical activity and mobility at baseline and to interpret the direction of effects following physical therapy in the participants with CP.

Physical therapy protocol

The participants with CP completed 24 gait training sessions under the direction of a licensed physical therapist. Each session lasted 1-hour and was performed three times a week over eight weeks. The overground gait training incorporated visuomotor tasks such as navigating obstacles with different heights, walking across a series of stepping-stones of variable distances, walking up and down stairs, and outdoor walking tasks that involved traversing various terrains. The respective tasks promoted problem-solving on how to best adjust the foot placements for a stable and efficient gait. Furthermore, the respective tasks were conducted at the participant's just right challenge point (Guadagnoli and Lee, 2004). Throughout the session, the physical therapist provided verbal feedback directed at fostering the participant's intrinsic recognition of the motor errors and instruction toward developing new foot placement strategies, with the implication that this would improve their ability to successfully complete the gait related tasks. Of note, the overground gait tasks incorporated in this investigation were very different from the mainstream approach of using a treadmill to increase the number of steps practiced (Borggraeve et al., 2010; Kurz et al., 2013; Bjornson et al., 2019). Such treadmill walking reduces the visuomotor experiences compared with stepping over and

around obstacles during the overground gait tasks used in this investigation.

MEG acquisition and experimental paradigm

All MEG recordings were conducted using a whole-head MEG system (MEGIN Neo, Helsinki, Finland) that was in a two-layer Vacuum-schmelze magnetically shielded room. The neuromagnetic responses during the experiment were sampled continuously at 1 kHz with an acquisition bandwidth of 0.1 – 330 Hz. During the experiment, the participants sat upright in a non-magnetic chair with their heads positioned within the helmet-shaped MEG sensor array. For the experiment, the participant was instructed to fixate on a grey circle on a black background that appeared on a projection screen that was 1 m away for 2000–2500 ms. The circle's color then changed to white and began flickering at 15 Hz (Fig. 1). The flickering stimuli were presented for 1500 ms with an interstimulus interval of 2000–2500 ms. The standard stimulus consisted of the white circle and this was augmented with eight oddball trials that were randomly intermixed and consisted of the same flickering visual stimulus, except the circle was blue. The purpose of the oddball trials was to ensure that participants attended to the visual stimuli. All participants were highly accurate in identifying the oddball stimulus.

MEG pre-processing and source imaging

Prior to the experiment, five coils were affixed to the participant's head and the location of the coils, three fiducial points, and the scalp surface were digitized (Fastrak, Polhemus Navigator Sciences, Colchester, VT, USA). During the MEG recording, an electric current with a unique frequency label (e.g., 322 Hz) was fed to each of the coils and was used to localize the head in reference to the MEG sensors. The participant's MEG data were subsequently co-registered with their individual MRI and transformed into standardized space. The high-resolution MPAGE T1-weighted images were obtained with a Siemens Prisma

scanner equipped with a 64-channel head coil using the following parameters: TR: 2400 ms; TE: 1.96 ms; flip angle = 8 deg; FOV: 256 mm; slice thickness: 1 mm slice with no gap; in-plane resolution: 1.0 mm³.

Each participant's MEG dataset was individually corrected for head motion that occurred during task performance using the MaxFilter software (MEGIN/Elekta). In addition, the signal space separation method with a temporal extension was used for noise reduction (Taulu and Simola, 2006). All MEG data pre-processing, co-registration, and source imaging were performed with the Brain Electrical Source Analysis (BESA) software (BESA v6.0; Grafelfing, Germany). Artifact rejection was based on an individualized fixed threshold method and supplemented with visual inspection. There were no statistical differences in the number of trials (i.e., baseline + stimuli) included in the final analysis after the artifact rejection step ($NT = 60.6 \pm 4.6$ trials, $CP_{pre} = 59.75 \pm 5.6$ trials, $CP_{post} = 61.6 \pm 3.2$ trials; $ps > 0.05$). The continuous magnetic time series were divided into epochs of 2300 ms in duration (–600 ms to 2900 ms), with the onset of the visual stimulus defined as 0.0 s and the baseline defined as –600 to 0 ms. Artifact-free epochs for each sensor were transformed into the time–frequency domain using complex demodulation and averaged over the respective trials (Kovach and Gander, 2016; Wiesman and Wilson, 2020). These sensor-level data were normalized to the mean power during the baseline, and the specific time–frequency windows selected for source imaging were determined by statistical analysis of the sensor-level spectrograms across the entire array of gradiometers from all participants (Ernst, 2004; Maris and Oostenveld, 2007; Wiesman and Wilson, 2020). Based on these time–frequency windows, a minimum variance vector beamformer was used to calculate the source power across the entire brain volume per participant at a 4.0 mm³ resolution (Gross et al., 2001). The source power in these images were normalized per subject using a separately averaged pre-stimulus noise period of equal duration and bandwidth (Van Veen et al., 1997; Hillebrand et al., 2005). It should be highlighted that the beamformer methods employed here don't use a priori regions of interest. Rather the algorithm calculates the power changes from baseline to active period across the entire brain.

Peak voxels were identified in the grand-averaged beamformer image and these were used for extracting virtual-sensor neural time series data per participant. Hence, the same voxel coordinates were used for all participants. The peak was selected for time series extraction because this is the most common approach in the literature and because the response strength declines rapidly from the peak and thus would reduce the fidelity of the signal if we averaged across the cluster or used an atlas. The virtual sensors were computed by applying the sensor weighting matrix derived through the forward computation to the pre-processed signal vector (Cheyne et al., 2006; Wiesman and Wilson, 2020). The virtual sensor time series represents the time-varying strength of the 15 Hz neural activity. Once the virtual sensors were extracted, they were transformed into the time–frequency domain, and the two orientations per peak voxel per individual were combined using the vector sum. The maximum relative power of the 15 Hz neural time series across the window of interest was the primary outcome variable of interest. Secondly, we also tested whether there were group differences in the latency of the 15 Hz response. This was computed by calculating the latency of when there was a 2 % positive change in the virtual sensor time course after the start of the visual stimulus presentation (e.g., 0 ms).

Clinical outcome measures

The participants with CP underwent a battery of pre- and post-gait training assessments that included a preferred 10-meter walking speed test (Oeffinger et al., 2008), Timed Up and Go assessment (TUG (Hassani et al., 2014)), and a Timed Up and Down Stairs assessment (Zaino et al., 2004). Three trials were completed for the 10-meter walking speed assessment, and the fastest speed across the respective trials was recorded. The TUG is a standard clinical test for assessing an individual's

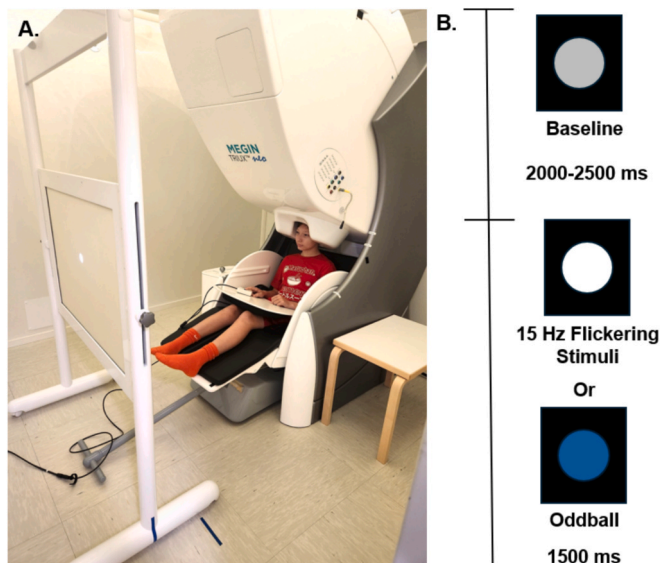


Fig. 1. Experimental paradigm. A. Depiction of the magnetoencephalographic (MEG) experimental setup for the visual entrainment task where the flickering stimulus was shown on a back-projected screen and the participant pressed a button with their right hand if an oddball was displayed. B. The paradigm consisted of a baseline period where a grey dot was displayed on the screen for 2000 to 2500 ms (randomly distributed), and a 1500 ms period where the participant viewed a 15 Hz flickering white stimulus or a blue oddball appeared on the screen. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

lower extremity strength and overall walking balance. For the TUG, the participant was instructed to stand-up from the bench, walk around a cone that was positioned 3 m away and return back to the bench. Participants completed the TUG test two times, and the fastest time was recorded. The timed up and down stairs required the participants to ascend and descend four steps three times as they would at home (i.e., using the railing, etc.) as quickly and safely as possible. Ascending/descending the stairs three times was representative of a full flight of 14 stairs and the time to complete the stairs was the outcome metric. All participants used the same assistive devices at the pre/post data collection time points.

In addition to the clinical metrics, the participants completed an outdoor walking course that was used as a surrogate measure to assess if the noted clinical mobility changes extend towards community-based walking activities. The 153 m outdoor course included real-world terrain changes such as uneven surfaces, inclines/declines and different surfaces (i.e., grass, bricks). The time to complete the course was the primary outcome variable, and the participants walked through the course the day before the actual pre- and post-data collections to familiarize themselves. All mobility assessments were completed with orthotics or assistive devices that the participant typically used for community ambulation.

Statistical analysis

An independent *t*-test was used to assess the hypothesis that compared with neurotypical controls, the youth with CP would display weaker occipital cortical activity at 15 Hz during the stimulation. We used separate paired *t*-tests to evaluate the hypotheses that after undergoing the visuomotor gait training paradigm, the youth with CP would have improvements in the strength of their occipital cortical activity and their performance on the respective clinical tests. Cohen's *d* effect sizes were calculated for the respective measures to gauge the magnitude of improvement in the clinical outcomes and cortical oscillations. An effect size of 0.2 was classified as a small and non-observable change, a 0.5 was a medium effect size associated with an observable clinical change, and effect sizes greater than 0.8 were classified as large and definitive clinical changes. Lastly, we used Spearman rho analyses to determine if there was a rank order correlation between changes in the strength of the cortical entrainment response and the observed changes in the respective clinical variables. A false discovery rate was used to adjust the alpha level to 0.03 for the respective *t*-tests and 0.04 for the correlations when assessing the respective hypotheses (Menyhart et al., 2021). Data presented in the text are displayed as the mean $\pm$ standard error of the mean.

Results

Clinical outcomes

Overall, the participants with CP had good compliance with 93 % of the gait training sessions completed. Sessions missed were related to weather and temporary sickness. There were no adverse events that occurred during the treatment. All pre/post MEG and clinical assessments occurred within one week prior and one week after completing the gait training.

The participants with CP had a 12 % improvement in their preferred walking speed (Fig. 2A; pre = 0.96 ± 0.07 m/s, post = 1.07 ± 0.06 m/s; $p = 0.001$, $d = -0.75$), a 16 % improvement in the TUG (Fig. 2B; pre = 10.9 ± 1.6 s, post = 9.1 ± 1.2 s; $p = 0.001$, $d = 0.76$), a 33 % improvement in the time to negotiate the stairs (Fig. 2C; pre = 64.8 ± 16.3 s, post = 43.6 ± 10.4 s; $p = 0.009$, $d = 0.52$), and a 12 % improvement in the time to complete the outdoor course (Fig. 2D; pre = 164.6 ± 31.9 s, post = 144.4 ± 28.0 s; $p = 0.016$, $d = 0.56$). The effect sizes for the respective clinical outcomes were medium to large, indicating that the overall mobility improvements seen across the

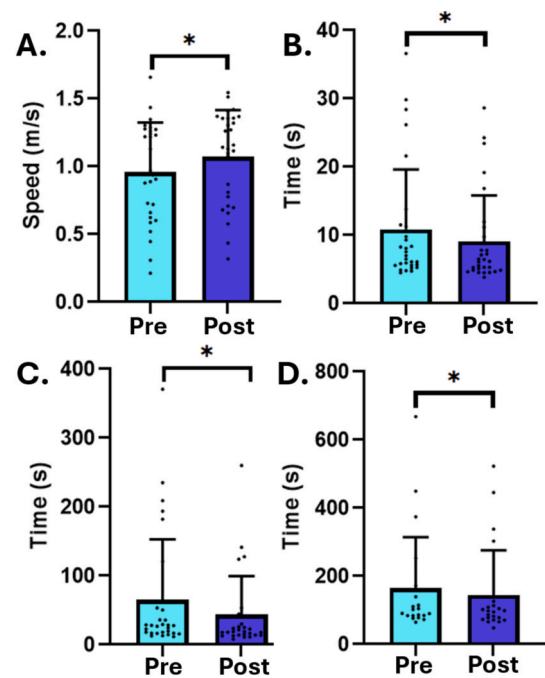


Fig. 2. Clinical outcomes measures. Bar graphs of the performance on the (A) 10-meter preferred walk test, (B) timed-up-and-go (TUG), (C) timed stairs test, and (D) time to walk a 150 m outdoor course at the pre- and post-gait training time points for those with cerebral palsy ($N = 29$). As shown, the group of participants displayed significant improvements across the respective clinical outcome variables. In the bar graphs, the points represent the participant values for the respective outcome measures, with speed in m/s units on the y-axis in (A) and time in seconds on the y-axis in (B–D). * $p \leq 0.03$.

participants after completing the gait training protocol were observable by the eye.

MEG sensor- and anatomical-space analyses

Visual inspection of the grand averaged oscillatory responses showed that there were prominent event related synchronizations (ERS) centered at the 15 Hz entrainment frequency in the sensors surrounding the occipital regions. Additional ERS responses were seen at the 30 and 45 Hz harmonics. Our statistical analyses of the sensor-level time–frequency spectrograms focused on the fundamental 15 Hz driving frequency since it was the frequency of the flickering stimulus. This analysis revealed a significant ERS across the 14–16 Hz frequency range ($P_s < 0.0001$, permutation corrected; Fig. 3A), with the strongest activity between 600 and 1200 ms. We subsequently used a beamformer to image the 14–16 Hz ERS seen in the 600–1200 ms time window with a -600 – 0 ms baseline. The resulting grand average maps indicated that the 14–16 Hz ERS was generated by neural populations in the occipital cortices (Fig. 3B).

Virtual sensor neural time series were subsequently extracted per participant and per visit in those with CP (i.e., pre/post gait training) from the peak voxel in the grand-averaged functional maps (Fig. 3B). Note that the peak voxel was the same across all participants and pre/post conditions, and the virtual sensor time courses use the same time window (e.g., 600–1200 ms) and baseline (-600 to 0 baseline) as the beamformed images. Additionally, the absolute power during the baseline period was not statistically different ($p \geq 0.05$) between groups or conditions (CPpre = 5.38 ± 1.4 nAm; CPpost = 8.84 ± 1.2 nAm; NT = 5.5 ± 1.8 nAm). Numerical inspection of the respective neural time courses suggests that the neurotypical controls had a stronger entrainment to the visual stimulus when compared with the persons with CP. Further, these numerical data suggest that the cortical response seen in

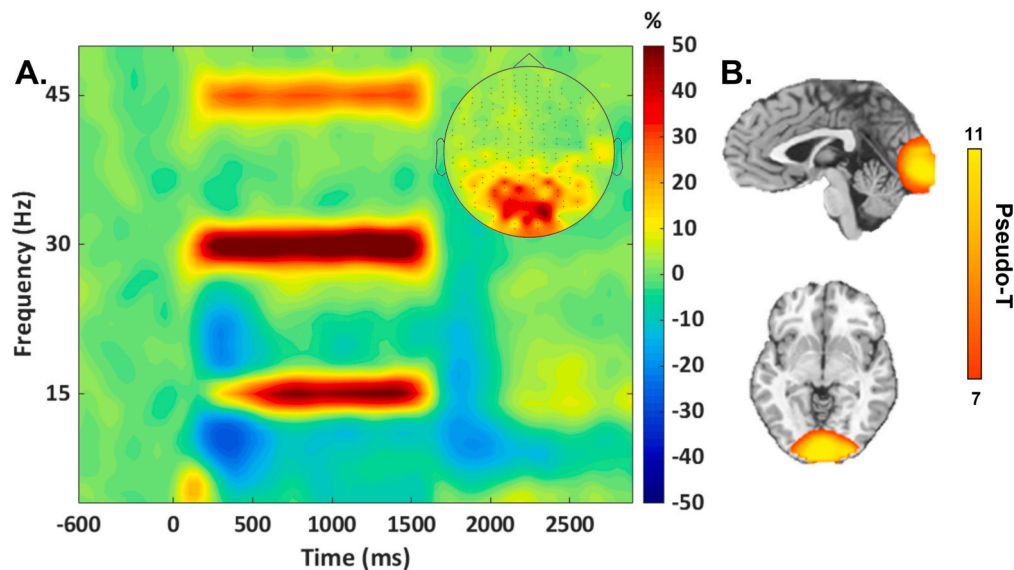


Fig. 3. Sensor-level time-frequency response. A.) Grand-averaged time frequency spectrogram from MEG sensor 2112 that was located over the occipital cortices. Frequency (Hz) is shown on the y-axis and time (ms) on the x-axis, with the units reflecting relative change (in %) from the baseline. As shown, there was a robust 14–16 Hz event related synchronization (ERS) after the onset of the stimulus (0 ms), which was sustained throughout the stimulus duration (1500 ms). Additional harmonics were seen around 30 and 45 Hz. The inset shows a topographical map that depicts the distribution of the 14–16 Hz increase seen across the respective magnetoencephalographic sensors. B) Beamformer images show that the 14–16 Hz ERS was present bilaterally in the occipital cortices.

the neurotypical controls continues to become stronger as the stimulus persists, while this doesn't appear to be the case for the persons with CP. The maximum amplitude during the beamformer time window was subsequently calculated (Fig. 4A) to statistically examine the group and treatment effects. Our results indicated that the 14–16 Hz ERS was weaker in the pre-therapy CP group compared to the neurotypical controls (pre = 20.4 ± 2.6 %; control = 43.4 ± 4.8 %; $p = 0.001$; Fig. 4B). Notably, there was an increase in the strength of the occipital ERS in the participants with CP after undergoing therapy (post = 26.3 ± 3.2 %; $p = 0.028$; $d = 0.43$; Fig. 4B), but the strength of the ERS still differed from neurotypical controls ($p = 0.006$). The effect

size of the therapeutic change in the strength of the 14–16 Hz ERS was medium ($r = 0.634$; $d = 0.43$), suggesting the improvement was meaningful. The onset of the ERS was also markedly delayed in the CP group relative to the neurotypical controls before therapy (pre = 313.79 ± 58.03 ms; control = 173.53 ± 30.97 ms; $p = 0.03$; Fig. 4C), and there was no change in the delay after the therapy (post = 350 ± 49.38 ms; $p > 0.03$).

Lastly, our statistical analyses revealed that there was a rank order correlation between the amount of pre- to post-therapy change in the preferred walking speed and that of the 14–16 Hz entrainment response ($\rho = 0.38$; $p = 0.04$) in participants with CP. This correlation indicates

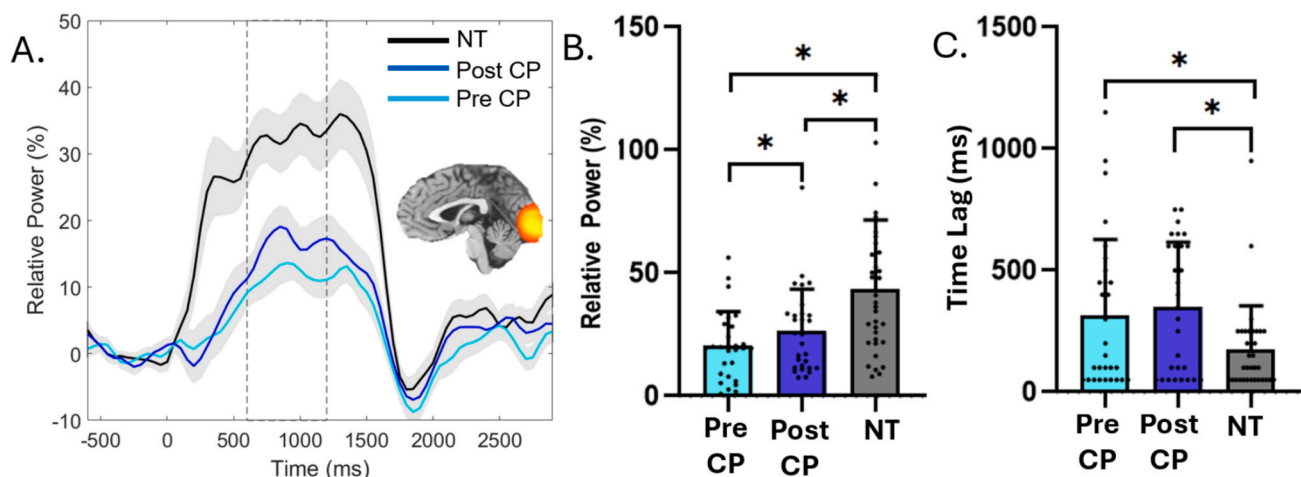


Fig. 4. Neural time series. A) Group- and visit-averaged neural time courses extracted from the peak voxel of the occipital cortices are shown in percent change from baseline units (i.e., relative power) on the y-axis and time on the x-axis. Onset of the flickering stimulus was at 0 ms and the 600 to 1200 ms time window imaged with the beamformer is highlighted by the dashed lines. The shaded area around the mean curves represents the standard error of the mean. The time series show that the strength of the entrainment to the flickering stimulus was notably weaker in the occipital cortices of the participants with cerebral palsy (CP) at both the pre- and post-therapy time points. However, the entrainment of occipital neural populations became significantly stronger after completing the gait training protocol and this change was toward the responses seen in the neurotypical controls (NT). B) Bar graphs of the maximum relative power seen in the 600–1200 ms window of the neural time course at the pre- and post-therapy time points. As shown, the relative power in the group with CP ($N = 29$) was weaker when compared with the neurotypical controls ($N = 24$) at both the pre- and post-therapy time points. However, the relative power was significantly stronger after therapy in those with CP. C) Bar graph of the time lag for the start of the entrainment in ms. Participants with CP had a greater time lag at the pre- and post-therapy time points when compared to the neurotypical controls. In the bar graphs, the points represent the participant values for the respective outcome measures. * $p \leq 0.03$.

that the participants with larger increases in preferred walking speeds after undergoing the gait training also tended to have greater changes in their occipital cortical entrainment index (Fig. 5). None of the other clinical variables were found to be significantly related to the strength of cortical entrainment ($p > 0.04$).

Discussion

Our prior MEG investigations have overwhelmingly shown that the occipital cortical oscillations of persons with CP are aberrant and linked with their uncharacteristic motor actions (VerMaas et al., 2019b, 2020, 2021; Kurz et al., 2020; Busboom et al., 2022). The primary purpose of this investigation was to determine if gait training has the potential to result in training-related changes in occipital cortical oscillations and motor outcomes in participants with CP. Our hypothesis that individuals with CP would display weaker entrainment of the occipital cortical oscillations when compared with neurotypical controls was verified, as was our hypothesis that the youth with CP would exhibit improvements in their occipital cortical oscillations after undergoing the gait training therapy. Likewise, we confirmed our hypothesis that individuals with CP would show improvements in their mobility after completing the physical therapy protocol. Lastly, our results indicated that these outcomes were related, as participants with greater increases in the strength of their occipital cortical responses following gait training tended to have larger improvements in their preferred walking speeds. Further discussion of the implications of these experimental outcomes is provided in the following sections.

Our results showed that the 14–16 Hz entrainment of occipital neural populations were markedly weaker and delayed in those with CP compared with the neurotypical controls. These outcomes clearly align with prior neuroimaging studies, and thus further support the view that individuals with CP have cortical visual processing impairments that possibly impact the fidelity of their movements (VerMaas et al., 2019b, 2020, 2021; Kurz et al., 2020; Busboom et al., 2022). We suspect that these cortical visual processing impairments partly stem from damage to the optic radiations of persons with CP, as these fibers neighbor regions of the corticospinal tracts that are frequently affected in those with CP (Schenk-Rootlieb et al., 1994; Ghate et al., 2016; Tinelli et al., 2020;

Araneda et al., 2022). An alternative perspective is that the altered visual processing seen in persons with CP might be related to the reduced movement experiences often reported in this patient population. For example, data from global positioning systems shows that the movement patterns of persons with CP within their neighborhood and/or city is reduced with increasing GMFCS levels (Kerfeld et al., 2021). In addition, youth with CP tend to have less movement within the classroom setting when compared with their peers (Ragonesi et al., 2010). Altogether the reduced mobility seen in those with CP might have cascading effects on the richness of their visuospatial environmental experiences, which could result in reduced integrity of early visual circuitry. Although these alternative conjectures are plausible, they have yet to be tested. Nevertheless, our results emphasize that greater attention should be placed on the possibility that aberrations in cortical visual processing may play a role in the aberrant motor actions seen in this patient population.

The gait training paradigm used in this investigation resulted in improvements in the overall mobility of the individuals with CP. Specifically, participants with CP displayed a faster-preferred walking speed, improved ability to negotiate stairs and faster completion of the TUG clinical assessment. The medium minimum clinically important difference (MCID) for the preferred walking speed is 0.1 m/s (Oeffinger et al., 2008) and 0.7 units for the TUG (Hassani et al., 2014). Hence, since the changes in the walking speed and TUG in this investigation exceeded these MCID values represented observable and clinically relevant mobility improvements. Importantly, participants with CP also demonstrated enhancements at the speed they were able to complete the outdoor course, suggesting that the clinical gains might have translated to the real-world. Altogether these clinical outcomes highlight the benefit of incorporating tasks that involve visual-motor integration, such as navigating obstacles of different heights and distances, traversing stairs and walking on various terrains. These types of activities challenge the participant's visuomotor problem solving skills for actively adjusting the gait kinematics to meet the task demands. We suspect that this treatment approach might result in larger clinical gains than what is seen for gait treatment approaches that solely use a treadmill (Borggraeve et al., 2010; Kurz et al., 2013; Bjornson et al., 2019). Our rationale is that treadmill gait training lacks the optical flow and visuomotor problem solving strategies that are necessary for real-world gait.

Remarkably, our MEG results revealed that participants with CP exhibited stronger occipital cortical oscillations after undergoing the gait training and that those with larger increases tended to have bigger improvements in preferred walking speeds after therapy. This implies that the gait training used in this investigation may have the potential to beneficially improve the visual processing in those with CP. These results are impactful as they imply that the cortical visual processing deficits seen in those with CP may be correctable with physical therapy. We suspect that these improvements were partially driven by the richness of the visuomotor experience and the unique visual task demands that were part of our gait training. Alternatively, the improvements seen here may have been related to enhancements in the extrinsic ocular motility (e.g., fixation, smooth pursuit and saccades) that we previously documented as being deficient in persons with CP (Galli et al., 2024). In other words, improvements in the eye motor control might have influenced the visual processing of the those with CP.

Although the outcomes of this investigation were enlightening, there are several limitations that should be taken into consideration when interpreting the results. For one, the sample in this investigation was heterogeneous and none had a prior diagnosis of a visual processing impairment. That being said, it is likely that some participants in our sample had diminished visual acuity, altered visual fields, and/or a cortical visual processing impairment since such conditions are common in CP. Therefore, it is possible that the changes we observed in occipital entrainment responses might partially reflect improved orienting toward the visual task (i.e., directing attention to visual stimulus) due to

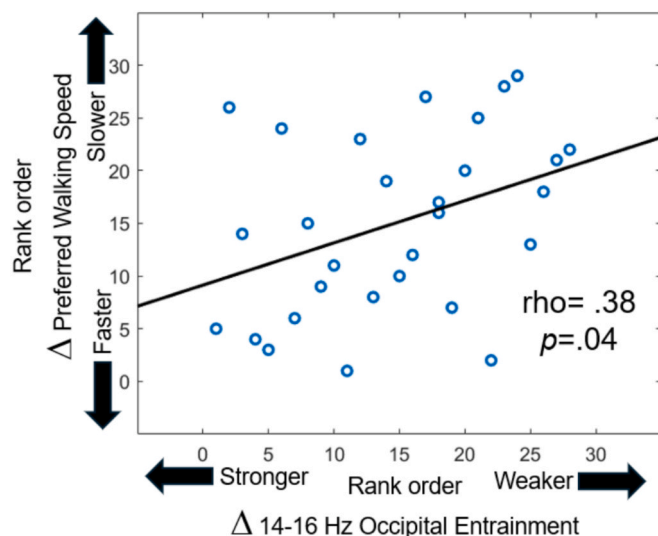


Fig. 5. Rank order correlation. Scatter plot of the rank order relationship between changes in the strength of the 14–16 Hz entrainment response in the occipital cortices and the change in preferred walking speed after the participants with cerebral palsy ($N = 29$) completed eight-weeks of gait training. The correlation indicates that individuals who have a larger increase in the entrainment response power also tended to have larger increases in walking speed after undergoing the gait training ($\rho = 0.38$; $p = 0.04$).

practice rather than a therapeutic effect. While this is possible, we believe that any such effect would be small for several reasons. First, we demonstrated a relationship between the extent of mobility improvements and changes in the strength of the occipital cortical oscillations after undergoing the gait training. This would not be expected if the neural entrainment change was solely due to practicing the task. Second, our experimental design included an oddball condition to ensure that the participants were attending to the stimulus, and we did not observe any changes pre- to post-therapy in the rate at which participants identified the oddballs. This suggests that they performed equally well on the task pre- to post-therapy. Nevertheless, we think this is an important consideration and that future investigations should include a clinical visual exam to assess the visual acuity of participants and/or eye tracking to monitor visual attention. An additional limitation to consider is that the gait training paradigm employed in this investigation incorporated visuomotor components, but wasn't exclusively a visual training paradigm *per se*. Potentially, treatment strategies that focus exclusively on training the visual system might have even larger results than what is shown here. This should be examined in future work, as the utility of the gait training paradigm used here for visual processing outcomes could be compared to gait training only in the treadmill environment. Lastly, this investigation did not have a therapeutic control group. Although the neurotypical controls provided useful data to assess baseline responses and interpret the direction of therapeutic changes, these data cannot establish whether pre- to post-therapy improvements were training-specific in those with CP. Future work should include a CP wait-list or alternative intervention arm, as the improvements observed here could partially reflect practice effects, nonspecific therapeutic influences, or greater attention to the visual stimulus. In addition, all of the participants and research staff were aware that participants were enrolled in a clinical trial and receiving an intervention. Nonetheless, our experimental outcomes are unique, as very few investigations have examined whether the altered occipital cortical activity in persons with CP can be mitigated by physical therapy, with parallel improvements in motor outcomes. At the very least, the potentially beneficial changes noted in this investigation motivate follow-up trials that test whether overground gait training promotes beneficial improvements in the mobility and occipital cortical activity of persons with CP.

Our prior MEG neuroimaging research has overwhelmingly shown that persons with CP have aberrant occipital cortical oscillations while viewing transient visual stimuli and performing visuomotor tasks. Despite these past reports, very few investigations have evaluated whether physical therapy can promote beneficial changes in these cortical occipital responses. Our results complement prior findings by showing aberrant occipital cortical activity in persons with CP during a visual entrainment paradigm involving a 15 Hz flickering stimulus. Importantly, our therapeutic results reveal that the occipital cortical activity can be improved through a gait training protocol that incorporates visuomotor task components, and that these beneficial neuroplastic changes parallel the overall mobility improvements seen in those with CP following therapy.

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CRediT authorship contribution statement

Max J. Kurz: Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Elizabeth Dao:** Writing – original draft, Formal analysis. **Morgan T. Busboom:** Writing – review & editing, Formal analysis, Data

curation. **Elizabeth Heinrichs-Graham:** Writing – review & editing, Visualization, Formal analysis. **Brad Corr:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Katie L. Bemis:** Writing – review & editing, Investigation, Data curation. **Logan White:** Writing – review & editing, Project administration, Data curation. **Kimberley S. Scott:** Writing – review & editing, Visualization, Supervision, Project administration. **Tony W. Wilson:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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