Children with cerebral palsy display altered neural oscillations within the visual MT/V5 cortices

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A B S T R A C T

Cortical visual processing in visual MT/V5 is necessary for tracking movement and performing reliable visuo-motor transformations. Although the role of this cortical area is well recognized, the activity of the visual MT/V5 cortical area in children with cerebral palsy (CP) has not been examined nor has its potential role in the atypical motor actions of these children been considered. This study used magnetoencephalography to image the neural activity in the motion-sensitive MT/V5 cortices of typically developing (TD) children ($n = 21$; mean age 14 yrs. $\pm$ 2, 12 males) and children with CP ($n = 21$; mean age 16 yrs. $\pm$ 4, 13 males) as they viewed a horizontally moving stimulus. Behavioral measures of visual perception were additionally assessed by having the participants press a button when the visual stimulus changed to moving in vertical direction. Our results showed that the horizontal movement of the visual stimulus evoked changes in the strength of the theta-alpha (5–10 Hz) and alpha-beta (8–20 Hz) oscillations in the visual MT/V5 area of all participants. Compared with the TD children, the children with CP had weaker alpha-beta oscillations in the visual MT/V5 cortices. In addition, the children with CP took longer to perceive a directional change of the visual stimulus and made more errors in detecting the change. Lastly, weaker alpha-beta oscillations were correlated with slower detection of the change in motion direction and less accuracy in identifying the change. This study shows that the uncharacteristic neural oscillations in the visual MT/V5 cortical area may partially account for the abnormal perceptions and motor decisions seen in children with CP.

1. Introduction

There is a growing consensus that visual dysfunction is possibly a core disorder among children with cerebral palsy (CP; Ego et al., 2015; Fazzi et al., 2012; Guzzetta et al., 2001). This dysfunction may result from an ocular pathology (e.g., acuity, retinopathy of prematurity, strabismus) and/or a brain-based pathology (e.g., visual perceptual impairment; Ego et al., 2015; Guzzetta et al., 2001). These visual perceptual abnormalities likely impact the motor decisions made by children with CP because online monitoring of a motor action involves integrating visual feedback with the other cortical areas (e.g., parietal and motor cortices), and extracting meaningful visual information for functional use (Born and Bradley, 2005).

Prior behavioral studies have identified that children with CP have a decreased sensitivity to visual motion, unrelated to the extent of their motor impairment (Pavlova et al., 2003). Several structural imaging studies have shown a possible link between the extent of the damage along the white matter tracts of the visual pathway in these children and their altered visual perceptual abilities (Martín et al., 2016; Schenk-Rootlieb et al., 1994; van den Hout et al., 2004). However, this connection is somewhat controversial given studies have also identified that some children with CP who have poor visual perception on clinical tests do not necessarily have identifiable structural brain abnormalities (Fazzi et al., 2009; Guzzetta et al., 2013; Schenk-Rootlieb et al., 1994). Potentially, the noted perceptual deficiencies seen in children with CP might be more dependent upon maladaptive neuroplasticity that results in aberrant activation of visual networks rather than the perinatal structural damage that these children may have incurred.

Several electroencephalographic (EEG) and magnetoencephalographic (MEG) studies of healthy adults have shown that the latency and amplitude of the evoked response in the visual MT/V5 cortical area are linked with the speed of the moving visual stimuli (Heinrich, 2007;

Kawakami et al., 2002; Maruyama et al., 2002). Specifically, these studies showed that as the speed of the moving visual stimuli increased, the latency of the neural response decreased and the amplitude of the evoked response increased in the visual MT/V5 area. Despite our enhanced understanding of the electrophysiology of these motion-sensitive cortices, these insights have yet to be employed to understand the visual perception deficits seen in children with CP.

Our recent MEG brain imaging results revealed that children with CP have altered cortical beta oscillations in the visual MT/V5 area when completing a visuomotor target force-matching task (Kurz et al., 2017a). This implies that the aberrant activity seen in this cortical area could play a partial role in the motor decisions of these children. The purpose of this study was to 1) directly examine visual MT/V5 activity in children with CP while viewing a moving stimulus, and 2) determine if there is a connection between the visual perceptions of these children and the strength of neural activity in the motion-sensitive MT/V5 region.

2. Materials and methods

2.1. Participants

Twenty-one children with CP (age = 15.7 ± 4 yrs.; 13 males; GMFCS levels I-IV; MACS levels I-IV) and 21 TD children (age = 14.0 ± 2 yrs.; 12 males) with no known neurological, developmental, musculoskeletal impairments participated in this study. All participants had normal or corrected to normal vision and no known visual processing impairments reported in their clinical records. In addition, none of the participants were on medication and none had been previously diagnosed with epilepsy or had an epileptic seizure. All of the parents provided written consent, and the children assented. The University of Nebraska Medical Center Institutional Review Board reviewed and approved this investigation.

2.2. MEG data acquisition and experimental paradigm

All recordings were conducted in a one-layer magnetically-shielded room with active shielding engaged for advanced environmental noise compensation. The children were seated upright in a magnetically silent chair with their head positioned within the helmet-shaped MEG sensor array. A custom-built head stabilization device that consisted of a series of inflatable airbags that surrounded the sides of the child's head and filled the void between the head and MEG helmet was worn during the data collection. This system stabilized the head and reduced the probability of any large medial/lateral and anterior/posterior head movements occurring during the data collections. Neuromagnetic responses were sampled continuously at 1 kHz with an acquisition bandwidth of 0.1–330 Hz an Elekta MEG system (Helsinki, Finland) with 306 magnetic sensors, including 204 planar gradiometers and 102 magnetometers.

During the experiment, the children viewed a visual stimulus that was displayed on a back-projected flat screen at eye-level and approximately one meter away. A custom C++/OpenGL visual MT/V5 stimulus program was created for this investigation. The stimulus consisted of an array of randomly positioned black dots behind a central red dot on a white background for maximum contrast (Fig. 1.). The children were instructed to fixate their gaze on the stationary red dot and to monitor for motion. The visual stimulus remained stationary for 2000 ms during the baseline period, followed by 1250 ms of fluid, linear visual motion that was created by the black dots cohesively updating their position every 250 ms. On 12% of trials, the black dots moved vertically, and the children were instructed to press a button with their right index finger as soon as they detected this motion. These vertical movement catch trials were not imaged and were used to behaviorally assess the child's perception of the visual motion. A short practice of the task was completed prior to the recording to ensure all children understood the task and were able to respond correctly. Each child completed a total of 120 horizontal trials to optimize the MEG signal-to-noise ratio. Throughout data acquisition, the children were monitored via real-time audio-video feeds from inside the shielded room.

2.3. MEG coregistration & structural MRI processing

Structural MRI data were acquired using a Siemens Skyra 3 T scanner. High-resolution T1-weighted sagittal images were obtained with a 32-channel head coil using a 3D fast field echo sequence with the following parameters: TR: 2400 ms; TE: 1.94 ms; flip angle = 8 deg.; FOV: 256 mm; slice thickness: 1 mm slice with no gap; in-plane resolution: $1.0 \times 1.0 \times 1.0$ mm.

For the MEG experiment, four coils were affixed to the head of the child and were used for continuous head localization. Prior to the experiment, the location of these coils, three fiducial points, and the scalp surface was digitized to determine their three-dimensional position (Fastrak 3SF0002, 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 four coils. This induced a measurable magnetic field and allowed each coil to be localized throughout the recording session. Since the coil locations were also known in head coordinates, all MEG measurements could be transformed into a common coordinate system. With this coordinate system (including the scalp surface points), each child's MEG data was coregistered with the native space neuroanatomical MRI data using the three external landmarks (i.e., fiducials) and the digitized scalp surface points prior to source space analyses. The neuroanatomical MRI data were aligned parallel to the anterior and posterior commissures and transformed into standardized space using BESA MRI (Version 2.0; BESA GmbH, Gräfelfing, Germany).

2.4. MEG pre-processing & time-frequency transformation

Each magnetic time series was individually corrected for head motion and was subjected to noise reduction using the signal space separation method with a temporal extension (Taulu and Simola, 2006). Cardio-artifacts from the remaining participants were removed from the magnetic time series using signal-space projection (Uusitalo and Ilmoniemi, 1997). The continuous magnetic time series were divided into epochs of 2100 ms in duration (−600 ms to +1500 ms, with time 0 defined as the onset of the visual motion), and the baseline period defined as −500 to −100 ms. Artifact rejection was performed using a fixed threshold method and supplemented with visual inspection. This quality check resulted in three of the participating children being excluded due to notable MEG artifacts. The epoch acceptance rate was 96% (e.g., 95.88 ± 5.86 epochs) for the remaining children.

Artifact-free epochs for each sensor were transformed into the time-frequency domain using complex demodulation and averaged over the respective trials. These sensor-level data were normalized by dividing the power value of each time-frequency bin by the respective bin's baseline power, which was calculated as the mean power during the baseline (−500 to −100 ms). The specific time-frequency windows used for imaging were determined by statistical analysis of the sensor-level spectrograms across the entire array of gradiometers. Each data point in the spectrogram was initially evaluated using a mass univariate approach based on the general linear model. To reduce the risk of false positive results while maintaining reasonable sensitivity, a two stage procedure was followed to control for Type 1 error. In the first stage, one-sample t-tests were conducted on each data point and the output spectrogram of t-values was thresholded at $p < 0.05$ to define time-frequency bins containing potentially significant oscillatory deviations across all participants. In stage two, time-frequency bins that survived the threshold were clustered with temporally and/or spectrally neighboring bins that were also above the ($p < 0.05$) threshold, and a cluster value was derived by summing all of the t-values of all data
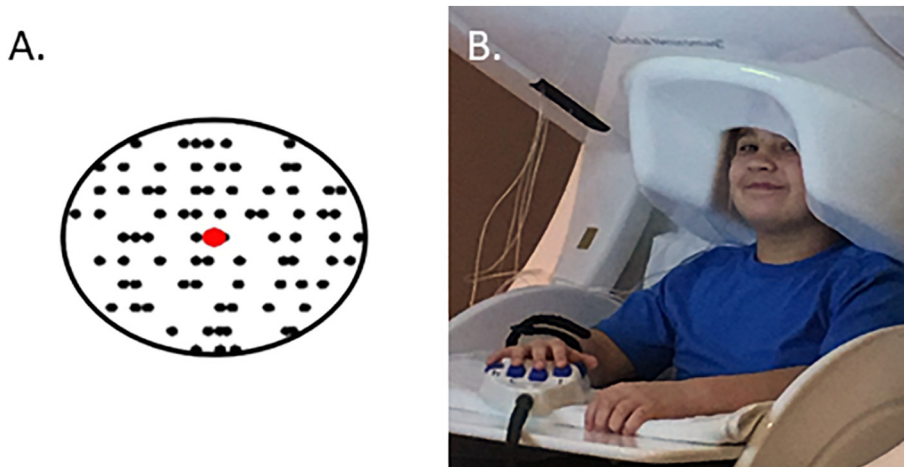
Fig. 1. A) The visual stimulus was continuously in view and consisted of a red central fixation dot surrounded by a random array of black dots. The child maintained visual fixation on the red dot while the visual stimulus remained stationary for 2000 ms, then the black dots moved cohesively horizontally or vertically for 1250 ms. B) The child pressed a button pad with the right finger when they detected that the visual stimulus was moving vertically instead of horizontally.

points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster-values and the significance level of the observed clusters (from stage one) were tested directly using this distribution (Ernst, 2004; Maris and Oostenveld, 2007). For each comparison, at least 10,000 permutations were computed to build a distribution of cluster values.

2.5. MEG source imaging & statistics

The dynamic imaging of coherent sources beamformer (DICS) was used to calculate the source power across the entire brain volume using spatial filters in the frequency domain and a single-shell spherical head model (Gross et al., 2001; Hillebrand et al., 2005; Van Veen et al., 1997). The single images were derived from the cross-spectral densities of all combinations of MEG sensors, and the solution of the forward problem for each location on a grid specified by input voxel space. Following convention, the source power in these images was normalized per subject using a separately averaged pre-stimulus noise period of equal duration and bandwidth (Hillebrand et al., 2005; Van Veen et al., 1997). The resulting beamformer images were 4.0 × 4.0 × 4.0 resolution and, since these were co-registered to each participant's native space T1-weighted anatomical MRI before beamforming, the images could be transformed into standard space by using the transform that was previously applied to the structural MRI volume and spatially then resampled. MEG pre-processing and imaging was performed with the Brain Electrical Source Analysis software (BESA v6.0; Grafelfing, Germany).

After all data were in standard space, neural activity in the visual MT/V5 cortical area was identified by applying a mask of the left and right visual MT/V5 areas using the Juelich Histological Atlas (Malikovic et al., 2007; Wilms et al., 2005) in FSL (Image Analysis Group, FMRIB, Oxford, UK). This mask was applied to the grand averaged beamformer images to identify the coordinates of the peak voxel in the left and right visual MT/V5 cortices. Subsequently, we extracted the time course of these voxels by applying the sensor-weighting matrix derived through the forward computation to the preprocessed signal vector. These "virtual sensor" extractions were completed for each hemisphere and then averaged, as our stimulus presentation was bilateral and we had no laterality hypotheses. Lastly, permutation testing was employed on the neural time series to identify the time windows where there were significant differences between the respective groups (Maris and Oostenveld, 2007).

2.6. Behavioral data

As stated in the preceding sections, for 12% of trials the visual stimulus moved vertically, and the children were instructed to press a button with their right index finger as soon as they detected this motion. These vertical movement catch trials were not imaged but were used to behaviorally assess the child's perception of the visual motion. Behavioral assessment of the child's visual perception were quantified using the output of a button pad, which was simultaneously collected during the MEG experiment at 1000 Hz. Reaction time was defined as the time difference between stimulus onset and when the button press occurred. Accuracy was calculated as the percentage of trials where the child correctly identified that the visual stimulus moved vertically. Group differences were analyzed with t-tests, and Pearson's correlations were used to determine if there was a relationship between the strength of the cortical oscillations, reaction time and accuracy.

3. Results

3.1. Behavioral results

Compared with the TD children, the children with CP had slower reaction times ($p < 0.001$ Fig. 2A) and were less accurate in identifying when the visual stimulus changed from a horizontal to vertical motion ($p = 0.002$; Fig. 2B). Together these behavioral results indicate that the children with CP were less able to perceive a change in the visual stimulus. Across all participants there was a strong negative correlation between reaction time and accuracy ($r = -0.71$, $p < 0.001$), suggesting that the children who had slower reaction times also tended to be less accurate in identifying that the visual stimulus had changed from horizontal to vertical motion.

3.2. Sensor-level results

When collapsing the data across the respective groups, the spectrograms showed that there were significant bursts of theta-alpha (5–10 Hz) activity and significant decreases in alpha-beta (8–20 Hz) across a cluster of gradiometers near the occipito-temporal region ($p < 0.001$, corrected; Fig. 3). The initial increase in the strength of the theta-alpha oscillations occurred shortly after the onset of the stimulus (50 ms) and was immediately followed by a decrease in the strength of the alpha-beta oscillations between 200 and 600 ms. In some MEG sensors, these changes in the neural oscillatory activity were repeated about every 250 ms and were time-locked with the updating of the visual stimulus. For illustrative purposes, we show group-averaged spectrograms for the TD children and children with CP separately in Fig. 3, but note that sensor-based statistics were computed by collapsing the data across all of the participants. Qualitative inspection of these figures shows differences in the strength of theta-alpha and alpha-beta oscillations between groups, with notably weaker activity in the children with CP.
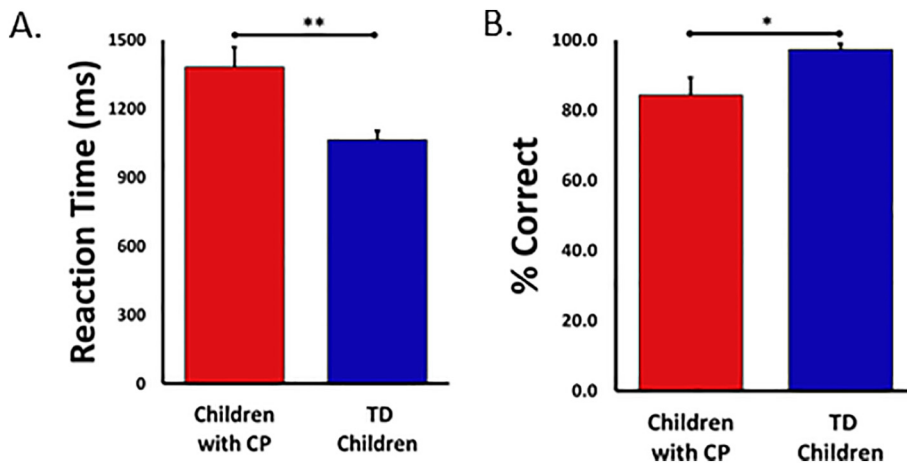
Fig. 2. A) Reaction time for the children with CP and TD children. Reaction time was calculated as the time difference between the onset of the vertically moving stimulus and the button press. As shown, the children with CP were slower to perceive a change in the motion direction (** indicates $p < 0.001$). B) Accuracy was determined by the percentage of trials where the visual stimulus was correctly identified when moving vertically. As shown, the children with CP made more errors in their perception of the motion of the visual stimulus (* indicates $p = 0.002$).

3.3. Source level and neural time course results

Both the increased theta-alpha (5–10 Hz) power within the 0 to 200 ms time window and the decreased alpha-beta (8–20 Hz) power within the 200 to 600 ms time window identified in the sensor-level analysis were imaged using a beamformer and an equal pre-stimulus baseline period between −500 to −100 ms. The resulting images were grand-averaged and revealed that the neural activity was spread bilaterally across the visual cortices. For both the theta-alpha and alpha-beta time-frequency windows, neural time courses were extracted from the peak voxels in the visual MT/V5 cortical areas of each hemisphere per participant and subsequently averaged across hemispheres (Fig. 4A). Permutation testing revealed that there were no significant differences ($p > 0.05$) in the strength of the theta-alpha neural time courses of the TD children and children with CP. Conversely, the amount of decrease seen in the alpha-beta neural time course during the 260–340 ms time window were significantly ($p < 0.001$) weaker for the children with CP when compared with the TD children (Fig. 4B).

To strengthen the veracity of our results, we examined whether there was differential head movement between groups and the potential impact on our findings. Our results indicated that children with CP had more vertical displacement of the head's position during the experiment compared to TD children (CP = 0.3 cm ± 0.2, TD = 0.2 cm ± 0.1, $p = 0.04$). However, the amount of vertical displacement did not correlate with the strength of the alpha-beta oscillations seen in the visual MT/V5 cortical area ($p = 0.5$). The lack of a correlation implies that the vertical displacement of the head during the experiment did not likely influence the results. Of note, we corrected for head movement, and aligned all data to the initial head position of the individual participant (at the start of the MEG session) prior to conducting our MEG sensor-level analyses. Thus, such differences in motion should be corrected for and not impact the final results, and this is precisely what we found.

3.4. Neurobehavioral correlations

The average of the decreased power in the alpha-beta frequency band across the 260–340 ms time window was subsequently calculated for each participant, and was used to evaluate if the amount of decrease in the alpha-beta cortical oscillations were linked with the child's visual perception. Using the data from all of the participants, there was a positive correlation between the magnitude of the decrease seen in alpha-beta oscillatory activity and reaction time ($r = 0.40$, $p = 0.012$),
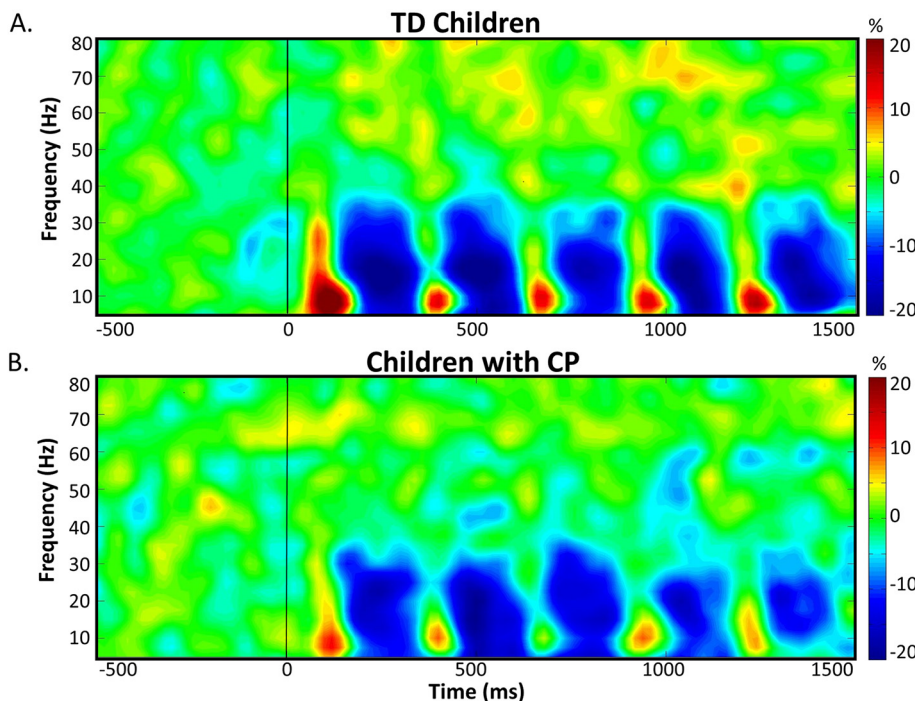

Fig. 3. Averaged time-frequency spectrograms for A.) TD children and B.) Children with CP during the visual motion stimulus. These plots were created from a gradiometer sensor located over the occipito-temporal cortical area. Time (in ms) is denoted on the x-axis, with 0 ms defined as the onset of the horizontally moving visual stimulus. Spectral power is expressed as the difference from the baseline period (−500 to −100 ms). As shown, there was a prominent series of increases in the strength of the theta-alpha band (5–10 Hz) oscillations and decreases in the strength of alpha-beta band (8–20 Hz) that occurred throughout the stimulus period and in some sensors were time-locked with the updating of the visual stimulus that occurred every 250 ms. Inspection of the respective figures reveals that the changes in the neural oscillations were weaker in the children with CP compared with the TD children.
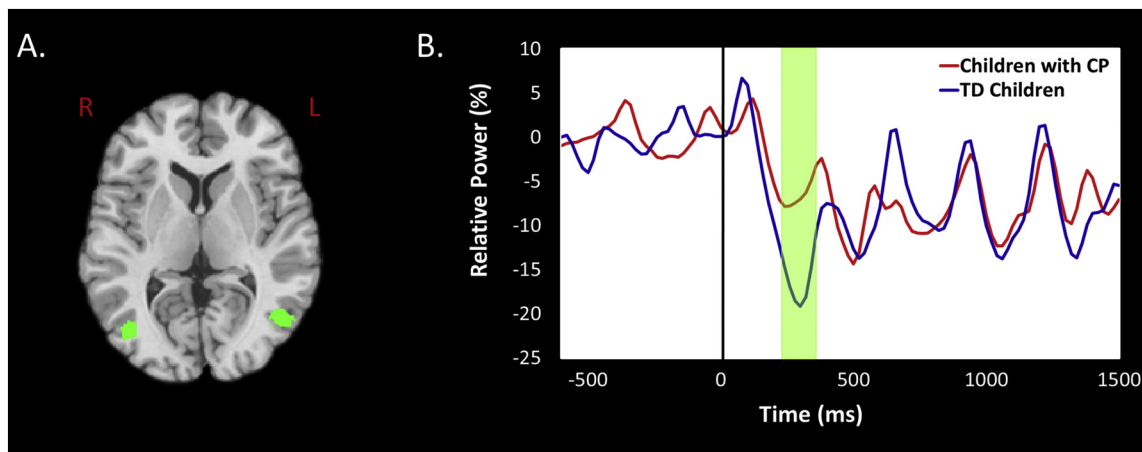
Fig. 4. A) Beamformer image showing averaged masked visual MT/V5 alpha-beta (8–20 Hz) cortical activity during the 200–600 ms time period of the visual stimulus. This image was used to identify the peak voxel in the visual MT/V5 cortical area across all of the participants. The neural time course in this peak voxel was subsequently extracted from the respective hemispheres and averaged. B) Neural activity at the alpha-beta frequency within the visual MT/V5 cortical area for the children with CP (red) and TD children (blue). Time (ms) is denoted on the *x*-axis, with 0 ms defined as the onset of visual motion and relative amplitude denoted on the *y*-axis. There were notable changes in the strength of the alpha-beta oscillations throughout the stimulus period that reoccurred every 250 ms. Compared with the TD children, the children with CP had weaker alpha-beta oscillations during the 240–360 ms time window ($p < 0.001$; green shaded area). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

which suggests that the children who had a smaller decrease in alpha-beta activity also tended to be slower in identifying change in the movement direction of the visual stimulus. Furthermore, there was a negative correlation between the strength of the decrease in alpha-beta activity and accuracy ($r = -0.33$; $p = 0.046$), implying that the children with smaller responses (decreases) tended to be less accurate in identifying the changes in movement direction.

4. Discussion

Despite the growing recognition that children with CP may have visual dysfunction, there is a significant knowledge gap in our understanding of the neurophysiological aberrations that underlie such perceptual dysfunction. The current study used MEG brain imaging to directly test the integrity cortical processing in the MT/V5 region of children with CP. Our experimental results indicated that compared with TD children, alpha-beta oscillatory activity within the motion-sensitive MT/V5 cortical area was weaker in children with CP. Furthermore, follow-up correlations suggest that these aberrant responses were at least partially linked with the atypical visual perceptions seen in children with CP.

Across both groups, there were prominent changes in the strength of alpha-beta oscillations in the MT/V5 region while viewing the moving visual stimulus. These results are in agreement with prior studies that have demonstrated that this region plays a key role in processing both real and apparent motion (Heinrich, 2007; Kawakami et al., 2002; Maruyama et al., 2002; Zihl and Heywood, 2015). Our results indicate that the decrease in the alpha-beta activity was notably weaker in the early time window (260–340 ms) for the children with CP, which implies that the MT/V5 cortical activity is atypical early in the processing stream. These early deficiencies likely play a prominent role in the visual processing deficits that are being reported in the clinical literature (Ego et al., 2015; Fazzi et al., 2012; Guzzetta et al., 2001; van den Hout et al., 2004). Furthermore, they extend our previous findings that have shown children with CP have weaker beta oscillations within the visual MT/V5 cortical area when performing a visuomotor task (Kurz et al., 2017a). Together with the results presented here, it appears that children with CP likely have visual processing deficits that influence their motor actions.

In the current study, the behavioral data strongly corroborated the brain imaging results by showing that the children with CP took longer

to perceive that there was a change in the direction of the visual stimulus (i.e., slower reaction times), and made more errors in deciding if the direction of the visual stimulus had actually changed. In addition, we identified that the children who had a weaker alpha-beta responses (less of a decrease) in MT/V5 during the early time window also tended to be slower in perceiving a change in the visual stimulus, and were less accurate in identifying when a change had occurred. These connections are intriguing because they imply that the uncharacteristic motor decisions seen in children with CP may not be completely dependent on the performance of the musculoskeletal system (Matthiasdottir et al., 2014; Moreau et al., 2012). Rather the motor decisions seen in these children are also partly dependent upon how they process and perceive visual information. This view fuels the emerging perspective that the abnormal motor actions seen in children with CP are fundamentally influenced by top-down processing (Gordon, 2016; Kurz et al., 2017a; Lust et al., 2018; Surkar et al., 2018).

None of the children with CP in the current study had a noticeable lesion near MT/V5 on their MRI, and thus no akinetopsia-like presentations were expected (Zihl and Heywood, 2015). However, this observation does not preclude the possibility that the altered cortical activity resulted from damage along the white matter tracks that comprise the dorsal visual pathways that are involved in the transmission of visual feedback. This notion is supported by prior imaging studies that have identified that disruption of the white matter tracts along the visual pathway in children with CP influences their performance on clinical assessments of visual perception (Martín et al., 2016; van den Hout et al., 2004). However, we are somewhat cautious on this inference because it is just as likely that the altered visual MT/V5 cortical activity might be a maladaptive neuroplastic change that was instigated by a lack of the visual experiences that infants and toddlers typically have through early exploration and mobility (Cole et al., 2016; Huang et al., 2014). This alternative explanation is supported by prior investigations that have that noted children with CP who have poor visual perception may not have identifiable structural brain abnormalities (Fazzi et al., 2009; Guzzetta et al., 2001; Pavlova et al., 2003; Schenk-Rootlieb et al., 1994).

5. Conclusion

The deficient visual perceptions seen in children with CP may in part be related to the uncharacteristic alpha-beta neural oscillations in

the motion-sensitive MT/V5 cortical area, and such aberrant oscillations likely impacts the motor decisions of these children. The results of this study further highlight the notion that the atypical motor actions observed in children with CP are not completely musculoskeletal centric, but rather also emerge from improper top-down processing of the ongoing sensory information. Our methodological approach for understanding the nature of the atypical motor actions seen in children with CP is unique because we combine visual motion and somato-motor components in a single experiment (Kurz et al., 2012, 2014, 2015, 2017a, 2017b). This approach is valuable because it is able to isolate and identify how aberrations in the respective sensory processing influences the motor decisions seen in children with CP.

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Declarations of interest

None.

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