Heliyon 8 (2022) e10545

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

A Val^{66}Met polymorphism is associated with weaker somatosensory cortical activity in individuals with cerebral palsy

Michael Trevarrow [a], Jennifer N. Sanmann [b], Tony W. Wilson [a,c], Max J. Kurz [a,c,*]

[a] Institute for Human Neuroscience, Boys Town National Research Hospital, Omaha, NE, USA
[b] Department of Genetic Medicine, Munroe-Meyer Institute, University of Nebraska Medical Center, Omaha, NE, USA
[c] Department of Pharmacology and Neuroscience, College of Medicine, Creighton University, Omaha, NE, USA

ARTICLE INFO

Keywords:
Sensorimotor
Lower extremity
Brain imaging
Neuroplasticity
Neurogenetics

ABSTRACT

Background: The brain-derived neurotrophic factor (BDNF) protein plays a prominent role in the capacity for neuroplastic change. However, a single nucleotide polymorphism at codon 66 of the *BDNF* gene results in significant reductions in neuroplastic change. Potentially, this polymorphism also contributes to the weaker somatosensory cortical activity that has been extensively reported in the neuroimaging literature on cerebral palsy (CP).

Aims: The primary objective of this study was to use magnetoencephalography (MEG) to probe if *BDNF* genotype affects the strength of the somatosensory-evoked cortical activity seen within individuals with CP.

Methods and procedures: and Procedures: Twenty individuals with CP and eighteen neurotypical controls participated. Standardized low resolution brain electromagnetic tomography (sLORETA) was used to image the somatosensory cortical activity evoked by stimulation of the tibial nerve. *BDNF* genotypes were determined from saliva samples.

Outcomes and results: The somatosensory cortical activity was weaker in individuals with CP compared to healthy controls ($P = 0.04$). The individuals with a Val66Met or Met66Met *BDNF* polymorphism also showed a reduced response compared to the individuals without the polymorphism ($P = 0.03$), had higher GMFCS levels ($P = 0.04$), and decreased walking velocity ($P = 0.05$).

Conclusions and implications: These results convey that *BDNF* genotype influences the strength of the somatosensory activity and mobility in individuals with CP.

What this paper adds: Previous literature has extensively documented altered sensorimotor cortical activity in individuals with CP, which ultimately contributes to the clinical deficits in sensorimotor processing documented in this population. While some individuals with CP see vast improvements in their sensorimotor functioning following therapeutic intervention, others are clear non-responders. The underlying basis for this discrepancy is not well understood. Our study is the first to identify that a polymorphism at the gene that codes for brain derived neurotrophic factor (BDNF), a protein well-known to be involved in the capacity for neuroplastic change, may influence the altered sensorimotor cortical activity within this population. Potentially, individuals with CP that have a polymorphism at the *BDNF* gene may reflect those that have difficulties in achieving beneficial outcomes following intervention. Thus, these individuals may require different therapeutic approaches in order to stimulate neuroplastic change and get similar benefits from therapy as their neurotypical peers.

1. Introduction

Cerebral palsy (CP) results from an insult to the developing brain [1], and it is one of the most costly neurological disorders in the United States, with a prevalence of approximately 3 out of every 1,000 children receiving a diagnosis [2, 3]. CP is marked with mobility issues stemming from increased muscle tone, hyperexcitable reflexes, spasticity, and joint contractures – with others experiencing hypotonia, dyskinesia, and ataxia as well [4]. Sensorimotor clinical deficits in motor planning and execution [5, 6, 7, 8, 9, 10, 11], as well as deficits in proprioception, stereognosis and tactile discrimination [5, 12, 13, 14, 15, 16, 17], have been consistently documented in this patient population. Currently, the results of treatment

* Corresponding author.
E-mail address: max.kurz@boystown.org (M.J. Kurz).

https://doi.org/10.1016/j.heliyon.2022.e10545
Received 9 September 2021; Received in revised form 21 June 2022; Accepted 31 August 2022

paradigms for individuals with CP are highly variable, with some individuals exhibiting extensive sensorimotor improvements following therapy, while others are clear non-responders [18]. Yet, the physiological factors responsible for this response variability remain unknown.

A major barrier to advancing our understanding of the variable treatment outcomes is the ideology that the response variability primarily resides in the musculoskeletal system, with less attention paid to the neurological factors that influence the potential for neuroplastic change [19]. Several studies have examined whether this response variability may be attributed to factors such as the corticospinal projection pattern, but the outcomes from these studies have been inconclusive [20, 21, 22, 23]. Recently, there has been a growing interest in identifying whether there are genetic factors that regulate the extent of the therapeutically driven neuroplasticity [24]. In particular, BDNF and variations at the *BDNF* gene have been suggested to play a role in neuroplasticity and motor performance. For example, animal models have shown that an up-regulation of BDNF occurs within the sensorimotor cortices after learning a new motor skill, and this is accompanied by reorganization of the sensorimotor cortical areas [25, 26]. Similarly, an inhibition of BDNF in the motor cortex hinders motor performance and results in decreased cortical reorganization [27]. These results reflect the critical role that BDNF plays in neuroplastic reorganization within the sensorimotor cortices that occurs while learning a new motor skill.

A single nucleotide polymorphism that produces a valine-to-methionine amino acid substitution at codon 66, at either one or both alleles in the human *BDNF* gene (Val66Met or Met66Met), has been shown to disrupt the protein's activity-dependent release, which in turn adversely impacts the capacity for neuroplastic change [28]. Approximately 30% of the general population has the Val66Met or Met66Met genetic polymorphism [29]. Prior fMRI studies have identified that individuals with the polymorphism tend to have a smaller volume of sensorimotor cortical activation [28]. This reduction is presumed to be related to the polymorphism's influence on the prevalence of BDNF. Prior transcranial magnetic stimulation (TMS) studies have also shown that healthy adults with the *BDNF* polymorphism exhibit less change in their motor-evoked potentials and cortical reorganization after practicing a motor skill [28, 30], as well as decreased ability to undergo motor improvements behaviorally after practicing a motor task [31]. Altogether these results clearly suggest that the BDNF polymorphism is a marker of reduced potential for neuroplasticity.

While these findings support the notion that neuroplasticity is adversely affected by the *BDNF* polymorphism, there is a paucity of studies investigating how the BDNF genotype may impact sensorimotor cortical activity in individuals with CP. Our laboratory and others have demonstrated that youth with CP have reduced somatosensory cortical activity in response to both electrical and tactile stimulation of the hand and foot mechanoreceptors [32, 33, 34, 35, 36, 37]. We posit that the weaker somatosensory cortical activity seen across these investigations may be partly driven by an individual's *BDNF* genotype. In other words, we hypothesize that those with the *BDNF* Val66Met or Met66Met genotype will have weaker somatosensory-evoked neural responses compared to those with the Val66Val genotype. To address this hypothesis, we used magnetoencephalographic (MEG) brain imaging to determine if the somatosensory-evoked cortical activity is different in individuals with CP that have the *BDNF* Val66Val genotype in comparison with the individuals that have the Val66Met or Met66Met genotypes. In addition, we examined a group of healthy controls to aid in the interpretation of our findings.

2. Materials and methods

2.1. Participants

The Institutional Review Board reviewed and approved this investigation. Informed consent was acquired from the adult participants and parents of the children's participants, and the children assented to participate in the experiment. Thirty-eight individuals participated in this neurogenetics investigation. Twenty of the participants had a diagnosis of spastic diplegic CP and eighteen were neurotypical (NT) controls (CP = 15.37 ± 5.52 years, Females = 10, GMFCS = I–IV; Healthy controls = 14.21 ± 2.51 years, Females = 5). The two groups did not significantly differ by age (P = 0.290). Participants were excluded according to MEG/MRI exclusionary criteria such metal implants, dental braces or permanent retainers, or other metallic or otherwise magnetic non-removable devices. The participants with CP also did not have orthopedic surgery or undergo Botulinum toxin injections within the last 6 months. Furthermore, none of the participants with CP had a dorsal rhizotomy or significant volume loss on their MRI. The participants with GMFCS levels of I and II typically ambulate independently, although with slowed gait speed and abnormal gait patterns [38]. Individuals with GMFCS level of III often require assistive devices to ambulate, such as crutches, ankle-foot orthoses, or wheelchairs. Individuals with GMFCS levels IV and V often require powered mobility devices.

2.2. BDNF genotyping

Saliva samples were collected from the participants with CP using the Oragene kit (DNA Genotek, Ottawa, Ontario, Canada). Genomic DNA was isolated according to standard laboratory procedures using a manual DNA extraction protocol and was quantified using the NanoDrop ND-1000® spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA). Polymerase chain reaction (PCR) amplification of the 274-bp fragment containing codon 66 of the *BDNF* gene (RefSeq NM_170735.5) was performed according to standard procedures (Sen et al., 2003). The PCR products were analyzed by direct sequence analysis in both the forward and reverse directions utilizing automated fluorescence dideoxy sequencing methods to determine the amino acid status at codon 66. Participants with the *BDNF* polymorphism included those with either the Val66Met or Met66Met genotype, while participants without the polymorphism had the Val66Val genotype.

2.3. MEG acquisition, preprocessing and source imaging

Note that the methods used in this study was similar to the analysis pipeline used in other studies that have evaluated somatosensory cortical activity using MEG [39, 40, 41, 42]. Neuromagnetic responses were sampled continuously at 1 kHz using an Elekta/MEGIN MEG system (Helsinki, Finland). A single pulse, unilateral electrical stimulation was applied using electrodes that were placed over the right tibial nerve, and the stimulation intensity was set to the individual's motor threshold. The stimulation was elicited once every 2 s for 4 min (e.g., 120 trials). The continuous magnetic time series was divided into epochs of 1100 m s duration, from -500 to 600 ms with the baseline being defined as -400 to -100 m s and 0.0 m s being stimulation onset. Epochs containing artifacts were rejected based on a visual inspection and a fixed-threshold method using individual amplitude and gradient thresholds. An independent samples t-test revealed that the number of trials accepted between groups was not significantly different (NT = 102.5 ± 2.92, CP = 106.4 ± 2.16, P = 0.28). The artifact-free epochs were averaged across trials to generate a mean time series per sensor. The specific time windows used for the source analysis were determined by statistical analysis of the sensor-level time series across both groups and the entire array of gradiometers [45]. Based on the sensor level statistical analysis, the time windows that contained significant events across all participants were used to guide time-domain source level analysis.

Structural MRI data were acquired using a Siemens Skyra 3T scanner and a 32-channel head coil (TR: 2400 m s; TE: 1.94 m s; flip angle = 8 deg; FOV: 256 mm; slice thickness: 1 mm slice with no gap; in-plane resolution: 1.0 mm^3). Subsequently, each participant's MEG data was coregistered with structural T1-weighted MRI data prior to source reconstruction. The time domain source images were computed using standardized low resolution brain electromagnetic tomography (sLORETA) [46]. The resulting whole-brain maps were 4-dimensional estimates

of current density per voxel, per time sample across the experimental epoch. These data were normalized to the sum of the noise covariance and theoretical signal covariance, and thus the units are arbitrary. Using the time windows identified in the sensor-level analysis, these maps were averaged over time following the somatosensory stimulation. These maps were then grand-averaged across the participants to determine the location of the peak voxel of the time-domain neural response to the stimuli across participants. From this peak voxel, the sLORETA units were extracted to derive estimates of the time-domain response amplitude for each participant. All imaging procedures were done with the Brain Electrical Source Analysis (BESA) software (BESA v7.0; Grafelfing, Germany). For additional methodological detail, please see our recent paper [41].

2.4. Mobility analysis

All participants were instructed to walk across a 5.75-m digital mat (GAITRite, Sparta, NJ) at their fast-as-possible walking speeds. The fast-as-possible walking speed was used since it provides a metric of the gait adaptability and provides a greater challenge to the participant's mobility. Each participant performed two trials and the fastest walking speed was used as the primary outcome measure. The mat digitized the locations of the feet, which were used to quantify the participant's spatiotemporal kinematics (velocity, step length, cadence).

2.5. Statistical analysis

Independent samples t-tests were used to evaluate whether the strength of the somatosensory-evoked activity and gait variables were different between the controls and participants with CP. Secondarily, one-way ANOVAs were used to determine whether there were significant differences in the strength of the somatosensory-evoked cortical activity and gait variables between the individuals with CP that had a polymorphism at the *BDNF* gene, individuals with CP that did not have a polymorphism at the *BDNF* gene, and the control group. Post hoc analyses used independent samples t-tests to determine group differences. All statistical tests were performed at the 0.05 alpha level.

3. Results

3.1. Genotyping outcomes

Of the individuals with CP, 70% were Val66Val genotype (N = 14; Age = 14.30 ± 4.90 years, Females = 6, GMFCS = I–IV), while 30% of the individuals with CP had at least one Met allele at codon 66 of *BDNF* (N = 6; Age = 17.86 ± 6.54 years, Females = 4, GMFCS = I–IV). These two groups did not significantly differ by age (P = 0.19).

3.2. MEG source imaging results

The permutation testing at the sensor level revealed two time periods of evoked activity that were significantly different from the baseline. The first began around 36 m s post stimulation and lasted until about 100 m s, and the second time period began around 164 m s and lasted until 252 m s. These time windows were used to focus the subsequent source imaging. The sLORETA images generated from the combined data from both groups revealed that the evoked-activity emanated from the leg region of the somatosensory cortices (Figure 1A). We subsequently determined the peak voxel of activity from the average image across all participants and extracted the neural time course for each individual. Consistent with past studies, qualitative inspection of the somatosensory neural time courses suggested that the individuals with CP exhibited weaker responses compared to controls (Figure 1B). Our statistical analysis revealed that the strength of the somatosensory response did not differ between the control group and all individuals with CP (Controls = 292.20 ± 38.06, CP = 248.85 ± 38.10, P = 0.428) during the first time window (36–100 m s). However, during the second time window (164–252 m s), the somatosensory-evoked cortical activity for the entire group of participants with CP was weaker than the controls (Controls = 273.73 ± 21.80, CP = 202.98 ± 24.23, P = 0.04).

Next, we wanted to further examine whether the somatosensory-evoked cortical activity during the second time window (164–252 m s) was weaker for the individuals with CP who had the *BDNF* polymorphism compared with those that had the Val66Val genotype. Our statistical analysis indicated that there was a significant group main effect for the

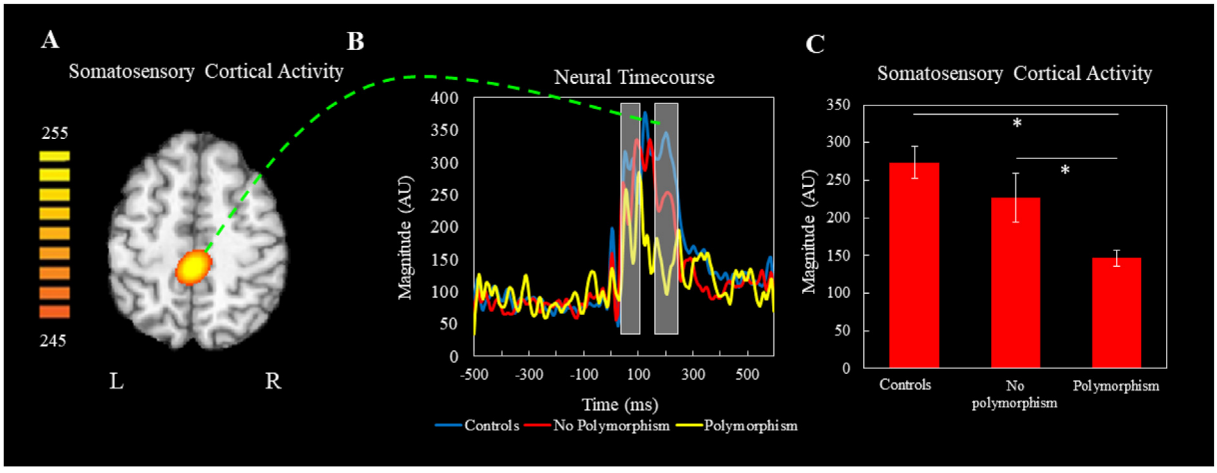

Figure 1. Somatosensory Cortical Activity. (A.) The somatosensory-evoked cortical activity emanated from the leg region of the contralateral (left) postcentral gyrus across all individuals. (B.) Source level neural time course depicting somatosensory-evoked cortical activity across the epoch. The tibial nerve stimulation occurred at time zero, and the gray boxes indicate the time windows used for analysis (36–100 m s and 164–252 m s), which were derived from the sensor level cluster-based permutation testing. The blue line represents the healthy controls, the red line represents the individuals with CP without a polymorphism at the BDNF gene, and the yellow line represents the individuals with CP who had a polymorphism at the BDNF gene. (C.) Bar graphs depicting the difference in magnitude of somatosensory-evoked cortical activity between the healthy controls, individuals with CP who had a polymorphism at the BDNF gene, and individuals with CP without a polymorphism at the BDNF gene during the second time window (164–252 m s). The individuals with CP who had a polymorphism at the BDNF gene had a significantly reduced somatosensory cortical response to tibial nerve stimulation in comparison to the individuals with CP without a polymorphism (P = 0.03) and the healthy controls (P < 0.01). Additionally, the healthy controls had a significantly greater cortical response than the individuals with CP altogether (P = 0.04).

magnitude of the somatosensory cortical response (P = 0.03). The post-hoc analyses revealed that the somatosensory-evoked cortical activity in the individuals with CP who had the *BDNF* polymorphism was significantly weaker than the activity in those who did not have the polymorphism (Val66Val = 227.05 ± 32.53, Val66Met and Met66Met = 146.83 ± 10.76, P = 0.03), and the controls (Controls = 273.73 ± 21.80, Val66Met and Met66Met = 146.83 ± 10.76, P < 0.01). Interestingly, the individuals with CP who did not have the polymorphism exhibited somatosensory cortical activity that did not statistically differ from the controls (Controls = 273.73 ± 21.80, Val66Val = 227.05 ± 32.53, P = 0.23; Figure 1C).

3.3. Clinical outcomes

The individuals that had the *BDNF* polymorphism tended to have higher GMFCS level scores (GMFCS = 2.83 ± 0.40) compared to those without the polymorphism (GMFCS = 1.79 ± 0.26; P = 0.04; Figure 2A).

Our biomechanical analysis of the spatiotemporal gait kinematics revealed that the individuals with CP overall had slower walking velocity in comparison to the controls (CP = 1.39 ± 0.11 m/s; controls = 1.91 ± 0.05 m/s; P < 0.01). Furthermore, our ANOVA revealed that there was a main effect of group for walking velocity (P < 0.01). Post hoc analysis revealed that the individuals with the *BDNF* polymorphism tended to have slower maximum walking velocity in comparison to the individuals without the polymorphism (Val66Val = 1.54 ± 0.10 m/s; Val66Met and Met66Met = 1.07 ± 0.24 m/s; P = 0.05), as well as the controls (controls = 1.91 ± 0.05 m/s; P = 0.02; Figure 2B). Additionally, the controls had faster walking velocity in comparison to the group without the polymorphism (Val66Val = 1.54 ± 0.10 m/s; P < 0.01).

The step length was also longer for the controls in comparison to the individuals with CP (CP = 0.62 ± 0.04 m; controls = 0.83 ± 0.03 m; P < 0.01). Our ANOVA revealed a significant main effect of group for step length (P < 0.01). The post hoc analysis showed that the controls (controls = 0.83 ± 0.03 m) had longer step lengths than the group with the polymorphism (Val66Met and Met66Met = 0.54 ± 0.10 m; P = 0.04) and without the polymorphism (Val/Val = 0.66 ± 0.04 m; P < 0.01), but the group of individuals with CP that had the polymorphism were not different from the group without the polymorphism (P = 0.16). Finally, cadence was not different between the controls compared with the individuals with CP (CP = 134.09 ± 7.64 steps/min, controls = 137.18 ± 3.91 steps/min, P = 0.71). There was also no significant main effect of group within the ANOVA for cadence (P = 0.128). Hence, the cadence was similar across the respective groups.

4. Discussion

Overall our experimental results are aligned with the numerous studies that have shown decreased somatosensory-evoked cortical activity in those with CP relative to neurotypical controls [5, 12, 16, 35, 36, 39, 47, 48, 49, 50], as well as the studies that have shown reduced oscillatory activity following somatosensory stimulation in those with CP [32, 33, 51]. Hence, there is mounting evidence that altered somatosensory cortical activity likely contributes to the sensory deficits that are largely reported in the clinical literature for this patient population [5, 13, 14, 15, 16]. Interestingly, the response was only weaker in the persons with CP during the latter portion. This is likely a result of the response being reduced in duration in the persons with CP, which can be seen qualitatively within the timeseries. Prior DTI studies have suggested that damage to the thalamocortical tracts is related to the somatosensory impairments seen in children with CP [37, 52, 53], and thus the abnormal activity within somatosensory cortices reported here may have been instigated by perinatal damage to the thalamocortical tracts. Potentially, this damage may alter the signal-to-noise ratio in such a way that the threshold for activation of the somatosensory cortices becomes aberrant and perhaps less responsive to important peripheral feedback. It is also conceivable that the decreased mobility in individuals with CP restricts interaction with the environment throughout development, which may result in altered development of the somatosensory system and, ultimately, the aberrant processing seen within the sensorimotor cortices. In support of this notion, prior studies have noted that the clinical motor and mobility impairments are highly related to the extent of the somatosensory deficits [5, 33, 34].

Our results show that approximately 30% of our sample had the *BDNF* Val66Met or Met66Met polymorphism, which is representative of what is seen in the general population [29]. Remarkably, the participants with the polymorphism had a more attenuated somatosensory-evoked cortical response in comparison to their peers with CP who did not have the *BDNF* polymorphism. Again, the group differences in somatosensory activity were found during the later time window. Qualitative analysis of the time series data suggests that the response duration was shortened in the group of individuals with the polymorphism. BDNF is a neurotrophic factor that supports a number of cellular functions, including neuronal resilience and survival. BDNF is transported to synapses, where it can modify neurotransmitter release, receptor sensitivity, and synaptic morphology [54, 55]. BDNF also improves neuroplasticity by stimulating synaptophysin and synaptobrevin synthesis to enhance synaptic transmission [54, 56] and plays a critical role in motor learning [25, 26]. The Val66Met and Met66Met nucleotide polymorphisms result in reduced activity-dependent release of the BDNF protein and consequently reduced capacity for these neuroplastic changes [28, 30]. Thus, we suspect that the individuals that had the *BDNF* polymorphism likely have a decreased capacity for neuroplastic change, resulting in further detriment to the development of the somatosensory system and ultimately a weaker somatosensory cortical response that is not sustained.

Individuals who had the *BDNF* polymorphism also tended to have higher GMFCS level scores and slower walking velocities than those without the polymorphism. This suggests that individuals with CP who have a more severe classification may be more likely to have the *BDNF* polymorphism. Based on the characteristics described in the previous paragraph, it is possible that the reduced BDNF in patients with the polymorphism may impact the ability to develop beneficial compensatory neural pathways after the initial perinatal neurological insult. Hence, there might be greater stability of the current brain networks and less susceptibility to change, which unfortunately would result in more

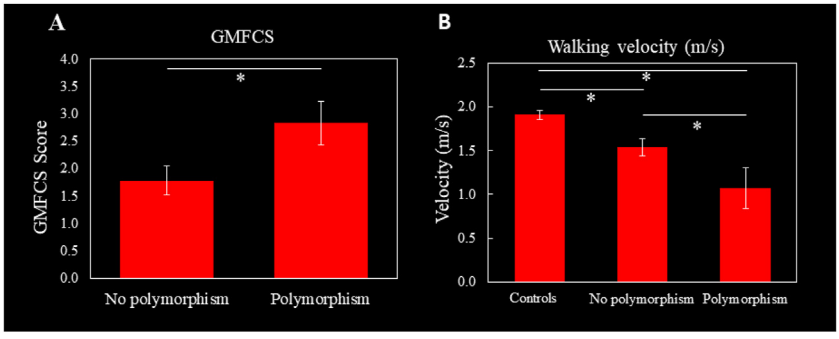

Figure 2. Walking Velocity and GMFCS Levels. Bar graphs representing the difference in GMFCS score (A) and walking velocity (B) between the individuals with CP who had the polymorphism at the BDNF gene, those who did not have the polymorphism, and the controls. Walking velocity was slower in those with the polymorphism (P = 0.05) and GMFCS scores were higher (P = 0.04) depicting decreased gross mobility in individuals with CP who have a polymorphism at the BDNF gene. The walking velocity was also higher in controls than both groups with CP (Ps < 0.05).

severe presentations and resistance to therapeutic gains that are thought to be implemented through adaptive plastic changes across the lifespan.

The ability of the brain to undergo neuroplastic change is essential to acquiring and refining new sensorimotor skills. Currently, there is a substantial portion of individuals with CP that do not respond well to therapeutic interventions, creating an urgency for steering treatment toward a more individualized approach. Potentially, this subpopulation of non-responders is made up of individuals that have the *BDNF* polymorphism. A reduction in capacity for neuroplastic change implies that these individuals may need increased therapy intensity or longer therapy sessions in order to stimulate the same neuroplastic change seen in those that do respond well to therapy. Alternatively, there has been recent interest in utilizing non-invasive brain stimulation to alter the resting state excitability of the neuronal populations within the sensorimotor cortices. This effectively primes the system and increases the capacity for neuroplastic change, which has been shown to be an effective strategy during neurorehabilitation [57]. Potentially, motor priming could be a means for increasing beneficial therapeutic outcomes in individuals with the polymorphism at the *BDNF* gene.

Before closing, it is worth noting some limitations of this study. As CP is inherently a heterogeneous disorder, it is possible that differences in the type of insult and resultant structural damage contributed to differences within the somatosensory cortical responses between groups. While prior work has illustrated that some individuals with CP might not display abnormal MRI findings [58, 59]. However, there is now a considerable literature showing that there are alterations in cortical volumes and morphometry (which are likely secondary in nature) in children with CP including in those where the predominant pathology appears to be in the white matter [60]. Thus, future work should further evaluate whether the type of insult incurred by persons with CP contributes to differences in somatosensory cortical activity. Furthermore, the BDNF literature is vast and spans other domains outside of the sensorimotor system. In particular, there is literature identifying that BDNF plays a role in aging, neurodegeneration, mental disorders, and other domains [61, 62, 63]. Therefore, it is possible that BDNF also affects the aging population in CP or influences the well-known cognitive impairments [64, 65]. These are prominent areas for future work to explore. Finally, our methodological approach of identifying responses at the sensor level to be analyzed at the source level allowed us to analyze the most robust responses (i.e., those detectable at the sensor level) but also potentially limited the sensitivity to subtler responses (i.e., the secondary somatosensory cortex). This is also an area for future work to explore by utilizing analytical approaches more suitable to identifying subtler responses.

5. Conclusions

In conclusion, somatosensory-evoked cortical activity demonstrated a stepwise pattern of aberrant activity, in which the individuals with CP showed weaker activity than the controls, and this aberrant activity was more pronounced in those with CP who had the *BDNF* polymorphism. The *BDNF* polymorphism decreases the capacity for neuroplastic change, which likely has downstream effects on the organization and development of the somatosensory cortices. Ultimately, these findings point toward a new understanding of the potential neuronal barriers that limit the ability of some individuals with CP to demonstrate clinically relevant improvements in their motor actions and somatosensory perception.

Declarations

Author contribution statement

Michael Trevarrow, Jennifer N. Sanmann: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Tony W. Wilson: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Max J. Kurz: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Funding statement

This work was supported by National Institutes of Health [R01-HD086245, R01-HD101833, R21-HD096390] and National Institute of Health funding source: 1P20GM144641-01.

Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

We would also like to thank Janet Williamson for her technical assistance with the genotyping assay.

References

[1] P. Rosenbaum, et al., A report: the definition and classification of cerebral palsy April 2006, Dev. Med. Child Neurol. Suppl. 109 (2007) 8–14.
[2] D. Christensen, et al., Prevalence of cerebral palsy, co-occurring autism spectrum disorders, and motor functioning - autism and Developmental Disabilities Monitoring Network, USA, 2008, Dev. Med. Child Neurol. 56 (1) (2014) 59–65.
[3] R.S. Kirby, et al., Prevalence and functioning of children with cerebral palsy in four areas of the United States in 2006: a report from the Autism and Developmental Disabilities Monitoring Network, Res. Dev. Disabil. 32 (2) (2011) 462–469.
[4] K. Oberhofer, et al., Subject-specific modelling of lower limb muscles in children with cerebral palsy, Clin. Biomech. 25 (1) (2010) 88–94.
[5] M.L. Auld, et al., Impact of tactile dysfunction on upper-limb motor performance in children with unilateral cerebral palsy, Arch. Phys. Med. Rehabil. 93 (4) (2012) 696–702.
[6] L. Sakzewski, J. Ziviani, R. Boyd, The relationship between unimanual capacity and bimanual performance in children with congenital hemiplegia, Dev. Med. Child Neurol. 52 (9) (2010) 811–816.
[7] D.A. Rosenbaum, et al., Time course of movement planning: selection of handgrips for object manipulation, J. Exp. Psychol. Learn. Mem. Cogn. 18 (5) (1992) 1058–1073.
[8] M. Mutsaarts, B. Steenbergen, H. Bekkering, Anticipatory planning deficits and task context effects in hemiparetic cerebral palsy, Exp. Brain Res. 172 (2) (2006) 151–162.
[9] C. Craje, et al., Compromised motor planning and motor imagery in right hemiparetic cerebral palsy, Res. Dev. Disabil. 31 (6) (2010) 1313–1322.
[10] A.M. Gordon, S.V. Duff, Fingertip forces during object manipulation in children with hemiplegic cerebral palsy. I: anticipatory scaling, Dev. Med. Child Neurol. 41 (3) (1999) 166–175.
[11] A. Gordon, J. Charles, S. Duff, Fingertip forces during object manipulation in children with hemiplegic cerebral palsy. II: bilateral coordination, Pediatr. Phys. Ther. 12 (4) (2000) 195–196.
[12] J. Cooper, et al., The determination of sensory deficits in children with hemiplegic cerebral palsy, J. Child Neurol. 10 (4) (1995) 300–309.
[13] K. Clayton, J.M. Fleming, J. Copley, Behavioral responses to tactile stimuli in children with cerebral palsy, Phys. Occup. Ther. Pediatr. 23 (1) (2003) 43–62.
[14] T.D. Sanger, S.N. Kukke, Abnormalities of tactile sensory function in children with dystonic and diplegic cerebral palsy, J. Child Neurol. 22 (3) (2007) 289–293.
[15] J.R. Wingert, et al., Tactile sensory abilities in cerebral palsy: deficits in roughness and object discrimination, Dev. Med. Child Neurol. 50 (11) (2008) 832–838.
[16] N.L. Maitre, Z.P. Barnett, A.P. Key, Novel assessment of cortical response to somatosensory stimuli in children with hemiparetic cerebral palsy, J. Child Neurol. 27 (10) (2012) 1276–1283.
[17] M.T. Robert, et al., Motor learning in children with hemiplegic cerebral palsy and the role of sensation in short-term motor training of goal-directed reaching, Dev. Med. Child Neurol. 55 (12) (2013) 1121–1128.
[18] I. Novak, et al., A systematic review of interventions for children with cerebral palsy: state of the evidence, Dev. Med. Child Neurol. 55 (10) (2013) 885–910.

[19] D.L. Damiano, Rehabilitative therapies in cerebral palsy: the good, the not as good, and the possible, J. Child Neurol. 24 (9) (2009) 1200–1204.
[20] N. Kuhnke, et al., Do patients with congenital hemiparesis and ipsilateral corticospinal projections respond differently to constraint-induced movement therapy? Dev. Med. Child Neurol. 50 (12) (2008) 898–903.
[21] H. Juenger, et al., Two types of exercise-induced neuroplasticity in congenital hemiparesis: a transcranial magnetic stimulation, functional MRI, and magnetoencephalography study, Dev. Med. Child Neurol. 55 (10) (2013) 941–951.
[22] M. Islam, et al., Is outcome of constraint-induced movement therapy in unilateral cerebral palsy dependent on corticomotor projection pattern and brain lesion characteristics? Dev. Med. Child Neurol. 56 (3) (2014) 252–258.
[23] A.R. Smorenburg, et al., Does corticospinal tract connectivity influence the response to intensive bimanual therapy in children with unilateral cerebral palsy? Neurorehabilitation Neural Repair 31 (3) (2017) 250–260.
[24] R. Diaz Heijtz, et al., Genetic variation in the dopamine system influences intervention outcome in children with cerebral palsy, EBioMedicine 28 (2018) 162–167.
[25] H. Ishibashi, et al., Tool-use learning induces BDNF expression in a selective portion of monkey anterior parietal cortex, Brain Res. Mol. Brain Res. 102 (1-2) (2002) 110–112.
[26] A.Y. Klintsova, et al., Altered expression of BDNF and its high-affinity receptor TrkB in response to complex motor learning and moderate exercise, Brain Res. 1028 (1) (2004) 92–104.
[27] J.A. Kleim, T.A. Jones, T. Schallert, Motor enrichment and the induction of plasticity before or after brain injury, Neurochem. Res. 28 (11) (2003) 1757–1769.
[28] S.A. McHughen, et al., BDNF val66met polymorphism influences motor system function in the human brain, Cerebr. Cortex 20 (5) (2010) 1254–1262.
[29] E. Shimizu, K. Hashimoto, M. Iyo, Ethnic difference of the BDNF 196G/A (val66met) polymorphism frequencies: the possibility to explain ethnic mental traits, Am. J. Med. Genet. B Neuropsychiatr. Genet. 126B (1) (2004) 122–123.
[30] J.A. Kleim, et al., BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex, Nat. Neurosci. 9 (6) (2006) 735–737.
[31] H. Devanne, et al., Afferent-induced facilitation of primary motor cortex excitability in the region controlling hand muscles in humans, Eur. J. Neurosci. 30 (3) (2009) 439–448.
[32] M.J. Kurz, et al., Children with cerebral palsy have uncharacteristic somatosensory cortical oscillations after stimulation of the hand mechanoreceptors, Neuroscience 305 (2015) 67–75.
[33] M.J. Kurz, et al., Aberrant synchrony in the somatosensory cortices predicts motor performance errors in children with cerebral palsy, J. Neurophysiol. 111 (3) (2014) 573–579.
[34] M.J. Kurz, et al., The magnitude of the somatosensory cortical activity is related to the mobility and strength impairments seen in children with cerebral palsy, J. Neurophysiol. 113 (9) (2015) 3143–3150.
[35] X. Guo, et al., Aberrant high-gamma oscillations in the somatosensory cortex of children with cerebral palsy: a meg study, Brain Dev. 34 (7) (2012) 576–583.
[36] C. Papadelis, et al., Cortical somatosensory reorganization in children with spastic cerebral palsy: a multimodal neuroimaging study, Front. Hum. Neurosci. 8 (2014) 725.
[37] C. Papadelis, et al., Reorganization of the somatosensory cortex in hemiplegic cerebral palsy associated with impaired sensory tracts, Neuroimage Clin 17 (2018) 198–212.
[38] R.J. Palisano, et al., Content validity of the expanded and revised gross motor function classification system, Dev. Med. Child Neurol. 50 (10) (2008) 744–750.
[39] M.P. Trevarrow, et al., The somatosensory cortical activity in individuals with cerebral palsy displays an aberrant developmental trajectory, J. Physiol. (2020).
[40] M.P. Trevarrow, et al., Altered somatosensory cortical activity is associated with cortical thickness in adults with cerebral palsy: multimodal evidence from MEG/sMRI, Cerebr. Cortex (2021).
[41] A.I. Wiesman, T.W. Wilson, Attention modulates the gating of primary somatosensory oscillations, Neuroimage 211 (2020), 116610.
[42] M.P. Trevarrow, et al., Val66Met polymorphism is associated with altered motor-related oscillatory activity in youth with cerebral palsy, Brain Sci. 12 (4) (2022).
[45] E. Maris, R. Oostenveld, Nonparametric statistical testing of EEG- and MEG-data, J. Neurosci. Methods 164 (1) (2007) 177–190.
[46] R.D. Pascual-Marqui, Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details, Methods Find Exp Clin Pharmacol, Spain, 2002, pp. 5–12.
[47] M.J. Kurz, T.W. Wilson, Neuromagnetic activity in the somatosensory cortices of children with cerebral palsy, Neurosci. Lett. 490 (1) (2011) 1–5.
[48] E.P. Teflioudi, et al., Somatosensory evoked potentials in children with bilateral spastic cerebral palsy, Pediatr. Neurol. 44 (3) (2011) 177–182.
[49] E.S. Park, et al., The effect of spasticity on cortical somatosensory-evoked potentials: changes of cortical somatosensory-evoked potentials after botulinum toxin type A injection, Arch. Phys. Med. Rehabil. 83 (11) (2002) 1592–1596.
[50] Y. Hirayama, et al., [Somatosensory evoked potential (SEP) to posterior tibial nerve stimulation in children with cerebral palsy], Rinsho Byori 47 (1) (1999) 76–82.
[51] M.J. Kurz, et al., Children with cerebral palsy hyper-gate somatosensory stimulations of the foot, Cerebr. Cortex 28 (7) (2018) 2431–2438.
[52] R. Trivedi, et al., Correlation of quantitative sensorimotor tractography with clinical grade of cerebral palsy, Neuroradiology 52 (8) (2010) 759–765.
[53] A.H. Hoon Jr., et al., Sensory and motor deficits in children with cerebral palsy born preterm correlate with diffusion tensor imaging abnormalities in thalamocortical pathways, Dev. Med. Child Neurol. 51 (9) (2009) 697–704.
[54] C.W. Cotman, N.C. Berchtold, Exercise: a behavioral intervention to enhance brain health and plasticity, Trends Neurosci. 25 (6) (2002) 295–301.
[55] Y.A. Barde, Neurotrophins: a family of proteins supporting the survival of neurons, Prog. Clin. Biol. Res. 390 (1994) 45–56.
[56] A.F. Schinder, M. Poo, The neurotrophin hypothesis for synaptic plasticity, Trends Neurosci. 23 (12) (2000) 639–645.
[57] M.E. Stoykov, S. Madhavan, Motor priming in neurorehabilitation, J. Neurol. Phys. Ther. 39 (1) (2015) 33–42.
[58] M. Bax, C. Tydeman, O. Flodmark, Clinical and MRI correlates of cerebral palsy: the European cerebral palsy study, JAMA 296 (13) (2006) 1602–1608.
[59] I. Krageloh-Mann, V. Horber, The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review, Dev. Med. Child Neurol. 49 (2) (2007) 144–151.
[60] A.M. Pagnozzi, et al., Alterations in regional shape on ipsilateral and contralateral cortex contrast in children with unilateral cerebral palsy and are predictive of multiple outcomes, Hum. Brain Mapp. 37 (10) (2016) 3588–3603.
[61] L.S. Hao, et al., Brain-derived neurotrophic factor as a biomarker for obsessive-compulsive disorder: a meta-analysis, J. Psychiatr. Res. 151 (2022) 676–682.
[62] N. Mehterov, et al., Interactions among brain-derived neurotrophic factor and neuroimmune pathways are key components of the major psychiatric disorders, Mol. Neurobiol. (2022).
[63] L. Tapia-Arancibia, et al., New insights into brain BDNF function in normal aging and Alzheimer disease, Brain Res. Rev. 59 (1) (2008) 201–220.
[64] M. Bax, et al., Proposed definition and classification of cerebral palsy, April 2005, Dev. Med. Child Neurol. 47 (8) (2005) 571–576.
[65] I. Novak, et al., Clinical prognostic messages from a systematic review on cerebral palsy, Pediatrics 130 (5) (2012) e1285–e1312.