Effect of sensory and motor connectivity on hand function in pediatric hemiplegia

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Abstract

Objective—We tested the hypothesis that somatosensory system injury would more strongly affect movement than motor system injury in children with unilateral cerebral palsy (USCP). This hypothesis was based on how somatosensory and corticospinal circuits adapt to injury during development: while the motor system can maintain connections to the impaired hand from the uninjured hemisphere, this doesn't occur in the somatosensory system. As a corollary, cortical injury strongly impairs sensory function, so we hypothesized that cortical lesions would impair hand function more than subcortical lesions.

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Methods—Twenty-four children with unilateral CP had physiological and anatomical measures of the motor and somatosensory systems and lesion classification. Motor physiology was performed with transcranial magnetic stimulation and somatosensory physiology with vibration-evoked EEG potentials. Tractography of the corticospinal tract and the medial lemniscus were performed with diffusion tensor imaging, and lesions were classified by MRI. Anatomical and physiological results were correlated with measures of hand function using two independent statistical methods.

Results—Children with disruptions in the somatosensory connectivity, and cortical lesions had the most severe upper extremity impairments, particularly somatosensory function. Motor system connectivity was significantly correlated with bimanual function, but not unimanual function or somatosensory function.

Interpretation—Both sensory and motor connectivity impact hand function in children with USCP. Somatosensory connectivity could be an important target for recovery of hand function in children with USCP.

Keywords

Somatosensory Evoked Potentials; Corticospinal Tract; Unilateral Spastic Cerebral Palsy

Introduction

Injury to the developing brain often results in impaired movement, known as cerebral palsy[1]. Injury to one hemisphere usually leads to unilateral spastic cerebral palsy (USCP), which primarily impairs hand function on the side opposite (contralateral) to the brain injury. Many studies of USCP have identified injury of the corticospinal tract (CST), the principal pathway for voluntary movement, as a determinant of upper extremity impairment[2]. Prior studies have shown that the CST integrity[2-4] and organization[5,6] correlate with hand function. In addition to movement deficits, an estimated 90% of children with USCP also have impaired somatosensory function[7]. Several studies have demonstrated correlations between the magnitude of somatosensory and movement impairments[8,9]. The close interaction of motor and sensory systems can make it challenging to determine their relative contribution to functional impairments. We interrogated anatomy and physiology of the CST and touch systems using homologous methods to determine their relative contribution to hand function.

A key determinant of the degree to which motor or somatosensory systems contribute to upper extremity impairment in USCP is the adaptation of each system to developmental brain injury. During normal development, the CST descends from motor cortex to establish bilateral connections to the spinal cord[10]. These bilateral projections are pruned through the third trimester and early childhood[11], leading to a predominantly contralateral system (Fig 1A). If brain injury occurs early in development or affects a large portion of the CST, early bilateral CST projections from the uninjured hemisphere persist, and the impaired hand is controlled via connections from the ipsilateral (uninjured) hemisphere[12] (Fig 1B and C). These ipsilateral connections, found in more than half of children with USCP, have the capacity to support substantial motor function[10,13, 14].

Somatosensory adaptation to injury is less robust[15-17] and differs from CST development in two important ways. First, axonal connections in the touch somatosensory system project almost entirely to one hemisphere, even after injury early in development[13]. Second, somatosensory axons can navigate around brain lesions that occur before the early third trimester to reach primary somatosensory cortex[12]. A common developmental brain injury affects periventricular (PV)[15,18] white matter. Thalamocortical projections can skirt PV lesions and reach their cortical target, albeit with decreased integrity[18-20]. In contrast, middle cerebral artery (MCA) infarcts are often large, occur later, and usually do not spare thalamocortical connections[18,19].

The relatively weak adaptation of the sensory system and the strong adaptation of the motor system to early injury leads us to the hypothesis that loss of somatosensory connections will more strongly correlate with upper extremity impairment than loss of contralateral motor connections. The impairments are predicted to be in both somatosensation and in movement. Further, we also hypothesized that hand function would be more impaired after MCA lesions than PV lesions, since MCA lesions are more likely to disrupt somatosensory circuits. Analyzing results by lesion will allow classification based on conventional and clinically indicated brain imaging. We tested these hypotheses by assessing anatomy and physiology of both the motor system and the somatosensory system in children with USCP.

Methods and Materials

2.1 Participants

Twenty-four children (13M/11F, average age 10.5±3.3, years.months) with congenital USCP participated (Table 1). The inclusion criteria were: congenital USCP, presence of hemiparesis that limits daily function, ability to lift arms 15 cm above table surface and grasp light objects, and enrolled in mainstream school. The exclusion criteria were: health problems that would interfere with participation (including visual impairment), seizures after 2 years of age, severe spasticity (Ashworth 3), hand surgery within one year, injection of botulinum toxin in upper extremity within six months, or metallic implants. Informed assent was obtained from participants and consent from parents/legal guardians. The research procedures were IRB approved by Burke Medical Research Institute, Teachers College (Columbia University), and Weill Cornell Medical College.

2.2 Experimental paradigms

Overview—In each participant, we measured the anatomy and physiology of the motor and the somatosensory system. Diffusion Tensor Imaging (DTI) was used to analyze the presence of motor and somatosensory tracts. Lesion type was analyzed using structural MRI. Somatosensory physiology was tested with somatosensory evoked potentials (SEPs)– stimulating the hand and measuring evoked potentials in the brain with electroencephalography (EEG). Motor physiology was tested with motor evoked potentials (MEPs) from single-pulse transcranial magnetic stimulation (TMS) of motor cortex and measuring hand muscle responses with electromyography (EMG).

EEG SEPs—31 channel EEG was recorded with NeuroPrax (NeuroConn, GmbH, Germany) data acquisition system at 4096Hz, referenced to the right mastoid. Vibrotactile stimulation was delivered to the pad of each index finger (Fig 2A) to preferentially stimulate the touch/proprioception system. The paradigm was designed based on previous studies[21]. Motors with 175Hz vibration frequency (1200 vibration trains of 100msec duration and 150-1300msec interstimulus-interval) were used to stimulate Pacinian corpuscles. 600 vibration trains were presented per hand, randomly distributed across the two hands. A transistor-transistor logic (TTL) pulse from the microcontroller was used to precisely mark the vibration onset in the EEG.

EEG was pre-processed with a 1-20Hz bandpass filter, downsampled to 512Hz and epoched into -100ms to 600ms trials relative to vibration onset. Trials with artifacts were automatically eliminated using pre-specified statistical metrics. The analysis procedure was defined by the challenges of processing brain injury pediatric EEG. Specifically, there were larger and more frequent artifacts and noise as the participants were young and tests were performed in an awake resting state. Additionally, we expected a lower signal-to-noise ratio and unspecific alterations in the spatial and temporal responses, due to neuroplastic changes. To limit subjectivity in analysis, we followed an objective procedural pipeline similar to previously published methods[22]. First we extracted relevant spatial filters using 31 channel EEG data for each hemisphere based on the largest invariance across the stimulation trials. This spatial filter was applied to the epoched data to extract the evoked response per trial. Next, a Riemannian geometry based classifier[23] was built to classify left vs. right hand evoked response in each hemisphere. Classification outcome was quantified as area-under-the-curve and controlled for over-fitting using Monte-Carlo cross-validation with repeated random sub-sampling. The significance was tested with a permutation method[24].

The goal was to categorize the presence or absence of an SEP from left versus right hand in the injured hemisphere, as determined by the classifier. SEPs in the unaffected hemisphere acted as a control; if a participant's SEP could not be significantly classified in the unaffected hemisphere, due to low signal-to-noise ratio, then the SEPs were categorized as 'undetermined' (n=3, Table 1). Participants' with significant classification of SEP in the unaffected hemisphere were classified as 'Present' if SEP in the affected hemisphere could be significantly classified, and 'Absent' otherwise.

TMS MEPs—Single-pulse TMS was used to analyze corticospinal pathways (Fig 2B). The participant's structural MRI was used to guide the TMS coil to the motor cortex, using neuronavigation (Brainsight) software. First, the region of the motor cortex that elicits the largest MEP was localized. Centered around this region, 3 concentric circular grids were created. Stimuli were delivered at each of these grid points in both hemispheres and the MEPs were recorded at the first dorsal interosseus and wrist flexor muscles, using bipolar surface EMG electrodes. An MEP was considered present if an EMG response ($>50\mu$V) was observed within 40msec. The pulses were delivered at 110% of the participant's resting motor threshold. The goal was to categorize the motor connectivity as *contralateral* vs. *ipsilateral.* This was accomplished with the Lateralization Index (LI)[25], defined as the percentage of the responsive sites for the affected hand, in the injured hemisphere compared to the total number of sites in both hemispheres. If more than 50% of total map area was

located in the injured hemisphere, LI>0.5, the participant was classified as having a contralateral CST, and ipsilateral otherwise.

DTI—DTI was used to construct motor and somatosensory tracts. The goal was to assess the presence or absence of motor and somatosensory fiber tracts from the injured and the uninjured hemisphere. 3T DTI scans were acquired with 75 slices (112x112 resolution) and 55 or 65 directions (b = 800s/mm^2). Deterministic tractography was performed with Diffusion Toolkit[26] using the 2nd-order Runge-Kutta fiber propagation method. TrackVis[26] was used to visualize the fractional anisotropy (FA) color maps to seed regions-of-interest (ROI) (Fig 2C). Motor (targeting CST[27], but would include the corticobulbar fibers as well) and somatosensory tracts (targeting the medial lemniscus)[27,28] were seeded using an axial slice of the pons on a DTI FA image that most clearly distinguished the tracts for the uninjured hemisphere. Tracts were then visually inspected in 3-D to ensure that they intersected the motor or sensory cortex. For reliability, D.G. and A.B. performed tractography independently and blindly. In the four participants who did not have visible somatosensory tracts on the lesioned side, we performed noise correction by excluding noisy images in DTI Studio[29]; tracts could not be reconstructed even after noise correction.

Structural MRI—High-resolution 176 slice (256x256) T1-weighted brain images were acquired with 3T MRI to characterize lesion type. Lesions were classified as a periventricular (PV), middle cerebral artery (MCA) or other (Fig 3), by a pediatric neurologist in consultation with a neuroradiologist as needed.

Tests of Hand Movement and Sensation—Five standardized tests were administered to analyze hand function. Unimanual dexterity was assessed with two tests: 1) Jebsen-Taylor Test of Hand Function (JTTHF)[30]: a timed test of 6 activities—flipping cards, object placement, simulated eating, stacking checkers, and transporting empty and full cans. 2) Box&Blocks[31]: measure the number of blocks moved between 2 boxes in 60 seconds. Bimanual dexterity was assessed with the Assisting Hand Assessment (AHA)[32]–structured play using both hands. Sensation was assessed with 1) Cooper Stereognosis[33]: a measure of the ability to recognize 10 objects placed in the hand with touch. and 2) Two-Point Discrimination[34]: which test the ability to discriminate 2 points placed 2-15mm apart. As these tests produce non-linear values we linearized and standardized all scores to a continuous scale between 0 (minimum) and 1 (maximum) to compare them. The transformation functions used were: AHA= score/100; Stereognosis= $(score/10)^2$; JTTHF= -$(log(score/1080))/4$; Box&Blocks= score/60; 2-Point= 1-$((score-2)/13)$. Raw and standardized scores are shown in Supplementary Table. For some participants (n=12), hand function measures were available from one timepoint. For others, scores and EEG from 2 timepoints were available and were averaged, to reduce measurement variability. AHA was our primary outcome because out of the available tests for children with hemiplegia, it best captures the use of impaired hand in daily activities, 2) it is robust, well-validated, and highly reliable.

2.3 Statistical Analysis

Standard univariate and multivariate analyses were performed to first investigate the relationship between the binary physiological and anatomical connectivity (present versus absent) and hand function. For all univariate analysis, significance was tested with a non-parametric permutation (5000 permutations) test[24] based on Welch's t-statistic suitable for unequal variance and sample sizes. To compare our five dependent response variables (Cooper, 2-Point, JTTHF, Box & Blocks, AHA), by each of our five binary factors (EEG, DTI somatosensory, TMS, DTI motor, lesion), we used a non-parametric one-way MANOVA[35] with permutation significance testing. The statistics were performed on the normalized data, but they were similar to outcomes from raw data (not shown). Sample sizes were: TMS (contra=9, ipsi=12), EEG (present=9, absent=9), DTI motor (present=8, absent=12), DTI sensory (present=16, absent=4), Lesion (PV=12, MCA=7). Effect size was computed with Cohen's d,(for univariate) and N^2 (for MANOVA).

Next, multiple linear regression and cluster analyses were used to test our hypothesis that somatosensory connectivity has a larger significant contribution to hand function than motor connectivity: 1) Relative contribution of motor and sensory physiology (independent variables) to each hand function test (dependent variable) was analyzed using multiple linear regression of sensory physiology (EEG) vs. motor physiology (TMS). Separately, we compared sensory anatomy (DTIs) vs. motor anatomy (DTIm) for each hand function test. 2) Correlation between the sensation and movement tests was analyzed with Spearman Rho. 3) We used a complementary and data-driven approach based on Cluster Analysis[36] to analyze the relative contributions of all measurements of connectivity (sensory and motor physiology, sensory and motor anatomy and lesion type) on hand function. Hand function tests were used to group participants into distinct groups. This was performed with a nonparametric dimension reduction visualization called t-distributed Stochastic Neighbor Embedding (t-SNE)[37], which compresses the 5 hand function tests into a 2-dimensional representation. This allows clustering of participants based on function. We then compared these clusters of hand function with the measures of anatomical and physiological connectivity and lesion type using k-means clustering. The goal was to determine whether measures of connectivity would segregate cluster of participants depending on their hand function. The fit between hand function clusters and connectivity measures was quantified with Cohen's kappa[38] (>0.75: excellent; 0.4-0.75: fair to good, and <0.40: poor).

3 Results

Table 1 summarizes participant demographics and test results.

Both sensory and motor connectivity correlate with hand function Sensory connectivity was assessed using anatomical and physiological measures. For sensory anatomy, DTI was used to determine whether the sensory pathway was present (n=16) or absent (n=4; Fig 2C). For sensory physiology, EEG was used to detect the presence of SEPs after vibrotactile stimulation of the index finger from each hand. SEPs were categorized as present (n=9) or absent (n=9; Fig 2A). For six children, EEG data had poor quality due to participant cooperation or technical issues.

There was a strong and significant association between sensory connectivity and hand function (Fig 4), with large effect sizes for SEPs (d=1.02-3.21) and DTI sensory (d= 0.92-2.34). Compared to children whose sensory tract was absent in the lesioned hemisphere by DTI, children who had an intact sensory tract had better movement and sensory ability of the impaired hand. Similarly, children whose SEP was present in the injured hemisphere had better movement and sensory ability than children without SEPs in the injured hemisphere. Multivariate analysis (MANOVA) of sensory connectivity across all 5 hand function tests showed significant difference of hand function in children with intact somatosensory connectivity (physiologically with SEPs and anatomically with DTI) versus those who did not (Table 2).

Motor connectivity was assessed using anatomical (DTI) and physiological (TMS) measures and compared with tests of hand function. Using DTI (Fig 2C), we determined if the CST was present (n=8) or absent (n=12). During TMS, we stimulated the injured and uninjured hemispheres and recorded MEPs in the FDI and wrist flexor muscles of the affected hand (Fig 2B). In 9 children, bilateral responses were found; these children were categorized as either predominantly ipsilateral or contralateral depending on which motor cortex had the greater number of responsive sites. Predominantly contralateral responses were found in 10 children, and predominantly ipsilateral responses in 12 children. In two of the younger children (participants 23 and 24), no MEPs in the impaired hand were evoked with stimulation of either hemisphere, which is common in young children[39].

Univariate analysis of TMS and DTI for each hand function test showed an association between motor connectivity and hand function, with smaller effect sizes (TMS d=0.49-1.19 and DTI motor d=0.48-1.21, Fig 4 and Table 2) than the corresponding somatosensory analysis. The presence of a contralateral TMS MEP was associated with significantly better performance on the AHA, but not with performance on any other test. Similarly, the presence of a contralateral CST, by DTI, was associated with significantly better performance in stereognosis, but not with performance on any other test. Multivariate analysis (MANOVA) of motor connectivity across all 5 hand function tests showed no significant difference of hand function for children who had intact anatomical connections by DTI or physiologically by TMS versus those who did not (Table 2).

To further test the influence of motor connectivity we performed additional analyses. We separated the children with the bilateral (where MEPs were evoked by TMS stimulation of both hemispheres (n=8) responses, from purely ipsilateral and purely contralateral, as performed in previous research studies [25]. Using 3 categories did not change the general trend of relationships with the hand function tests. They were however underpowered to test for significance. We also assessed the correlation of the continuous LI values with the hand function tests and it was not found to be significantly correlated with JTTHF, Box & Blocks, 2-point at p<0.05, while it was significantly correlated with AHA and Stereognosis (both p<0.05).

Type of lesion correlates with hand function

Among 24 participants, 12 had clearly identifiable PV lesions, and 7 had lesions in the middle cerebral artery territory involving cortex. Three children had more complex lesions

that could not be categorized as PV or MCA, while two children did not have an MRI. We hypothesized that impairments would be more severe in children with MCA lesion for two reasons. First these lesions often occur after the somatosensory tracts have been established, making them unable to skirt the lesion as has been observed for PV lesions. Second, these lesions often involve somatosensory cortex, which is critical for several sensory functions.

The impact of lesion type on hand function with univariate analysis is shown in Fig 5, and Table 2. Children with PV lesions had significantly better hand function scores than children with MCA lesions on all tests, except Box & Blocks. The effect size was moderate (d=0.76-2.00). Multivariate analysis (MANOVA) of lesion type (PV versus MCA) across the 5 hand function tests showed significant difference in hand function for children who had PV lesions versus those who had MCA (Table 2).

Furthermore, we observe that lesion type was significantly associated with the state of functional somatosensory connectivity but not anatomical connectivity. 84% of participants with MCA lesions had absent SEPs, compared to 12% ~~of~~ with PV lesions (Fisher's Exact Test shows a statistically significant difference between these groups, **p= 0.0163**). Sensory DTI tracts were absent in 43% of participants with MCA lesions compared to 9% PV lesions (p= 0.137). Similarly, 100% of participants with MCA lesions had TMS ipsilateral connectivity compared to 37% with PV lesions (**p= 0.0288**). However, DTI motor tracts were absent in 85% of participants with MCA lesions and 83% of those with PV lesions (p= 0.112). This discrepancy between anatomy and physiology highlights the possibility that during recovery, structural tracts (anatomy) may be present, but not necessarily functional (physiology).

Relative contributions of motor and sensory connectivity and lesion type to hand function

The above univariate and multivariate analysis showed that the sensory physiology and anatomy and lesion type each significantly and independently correlated with hand function. In contrast, no significant effect was observed for motor physiology and anatomy on hand function. Next we compared the contribution of motor and sensory connectivity on hand function.

First, we used a model-based approach (multiple linear regression) to analyze the relative contribution of sensory and motor physiology and anatomy to hand function. This differs from the previous analyses where only a correlation between connectivity and function was tested. For physiology, comparing sensory physiology (EEG) vs motor physiology (TMS) (Table 2. B1), sensory physiology had a statistically significant contribution towards movement (JTHHF) and sensation tests (Stereognosis and 2-Point) (p< 0.05 for all) and had large effect sizes for all. In comparison, motor physiology did not have a statistically significant contribution for any of the 5 tests. For anatomy, comparing sensory anatomy (DTIs) vs. motor anatomy (DTIm) (Table 2. B2), sensory anatomy had a statistically significant contribution to sensory hand function tests (Stereognosis and 2-Point) with large effect sizes, while motor anatomy did not show contributions towards any of the 5 hand function tests.

Second, we assessed the correlation between the movement and sensation hand function tests. We found significant correlations between all pairs of movement and sensation tests ($p<0.001$ for all pairs) (Fig 6B).

Third, we used a data-driven approach to find possible distinct groups based only on the hand function tests, rather than the sensory-motor anatomy or physiology. The t-SNE based visualization of the 5-dimension data (i.e., each movement and sensation test) in 2-dimensions revealed two highly distinct groups of comparable size (Fig 6A). To interpret the relationship of these groups with the hand function, we applied a k-means clustering, setting k= 2. To observe the relationship of these clusters and the hand function tests, we labeled the 2 clusters obtained from k-means clustering in all possible pairs of hand function test plots (shown as open and closed circles in Fig 6B). The clusters were found automatically in 2 quadrants: the upper right quadrant (good function) and the lower left quadrant (poor function). This segregation was stronger for the sensation tests than for the movement tests, as seen in the separation between the clustered participant groups in Fig 6B.

Then we determined how well each of the 5 measurement modalities (i.e. the motor and sensory anatomy and physiology plus lesion location) explained whether participants fall into these good versus poor function clusters. We measured agreement of each measurement category (absent/present for DTI and EEG, ipsi/contra for TMS, or PV/MCA for lesion) with the clusters using Cohen's kappa coefficient. As shown in Fig 6C, clusters strongly agree with the physiological somatosensory connectivity (EEG SEPs, kappa=0.85), fairly well with lesion and anatomical somatosensory categorization (kappa=0.59 and 0.50 respectively), and poorly with motor anatomy and physiology (kappa=0.37 and 0.37 respectively).

Thus, the above independent statistical procedures (univariate and multivariate analysis, multiple regression analyses and cluster analyses) all support the hypothesis that somatosensory connectivity (anatomy and physiology) is strongly correlated with hand function and has a larger relative contribution towards hand function compared to motor connectivity. In addition, lesion type strongly correlates with hand function as well; with MCA lesions associated with poor hand function and PV lesions with better hand function.

Discussion

Loss of somatosensory connectivity was strongly correlated with impairments of hand function in children with USCP. Motor connectivity was associated with impairments in bimanual function in children with USCP. Connectivity was determined using DTI for both the motor and somatosensory tracts. This outcome was achieved because we were able to assess the physiology and anatomy of these two systems and hand function in the same set of children. In addition, our procedures to extract the SEPs allowed detection of responses that can elude other detection methods. In particular, we presented a large number of trials in a short time and employed machine learning techniques to extract information from the EEG with relatively lower signal-to-noise ratio and spatio-temporal alterations in the neural responses due to developmental plasticity. Finally, the statistical and clustering methods employed supported the main hypothesis through two independent and objective measures.

Developmental response to injury

The main findings of our study can be understood in the context of the developmental response to injury. Participants with cortical damage tended to lack a classifiable SEP in the injured hemisphere, while participants with a subcortical lesion tended to have a classifiable SEP. This dichotomized relationship between lesion type and the somatosensory response supports our current working model. As illustrated in Fig 1B and C, the somatosensory connectivity is less likely to be affected in an early injury, such as a PV lesion, as these tracts are still developing and can skirt the lesion and reach the cortex. However, the established somatosensory connectivity is more likely to be disrupted in later injuries, such as the larger MCA lesions. The somatosensory connections do not have bilateral connections that might persist after unilateral injury, as the corticospinal system does.

These differences in the developmental alteration of the motor and somatosensory systems, often leads to motor control in the uninjured hemisphere and somatosensory function in the injured hemisphere (such as for participants 1-5). We thought that the two functions being segregated in opposite hemispheres would have a strong adverse effect on hand function, as these systems are highly interdependent. However, the effect of motor control for the affected hand being in the opposite hemisphere from somatosensory control was rather weak (i.e. no significant cross-effect). This suggests that ipsilateral motor control, while less optimal than typical contralateral control, may be a promising developmental alteration, even if sensory function is encoded in the opposite hemisphere. However, the integrity of the less adaptable somatosensory connections was significantly correlated with hand function. This implies that despite the motor adaptation, the integrity of the somatosensory connections had a relatively larger implication for the hand function. Developmental preservation of bilateral connections observed in children might make them less reliant on crossed CST connections than adults. This may help to explain why loss of CST connections may have a relatively weaker effect on hand function in children compared with adults[40].

Limitations

The main limitation of the study is that it has relatively small number of participants, with heterogeneities in the time, size and location of injury. Nevertheless, we see significant contribution of the somatosensory system to hand function with large effect sizes (d=1.0 to 3.2). A larger cohort with more participants in each subgroup might make the outcomes more statistically significant, especially in case of the motor connectivity analysis which had relatively smaller effect sizes (d=0.5 to 1.2). Indeed, our group[25] and others[41] have shown that CST connectivity is significantly associated with hand function. In this study, many children had both contralateral and ipsilateral CSTs. In other studies, these children with a bilateral CST have been analyzed separately than children with purely contralateral or ipsilateral CSTs. In the current study, there was insufficient power to analyze children with bilateral CSTs separately. Thus, we categorized children as having an ipsilateral CST if a majority of the map was located in the hemisphere ipsilateral to the affected hand. Four of thirteen children categorized as ipsilateral had a contralateral CST. Analysis of larger groups of children with different patterns of connectivity can help better elucidate the relationship to hand control.

Moreover, studies about the relationship between hand function and time/type or site of injury, attribute the early anatomical injury to the individual's *current* state of hand function as measured by hand function tests. This does not take into account interventions, compensatory strategies, or other neurological impairments, which can have an impact on hand function[42]. However, despite this expected variation we observed a significant overall impact of lesion type on hand function in a small participant group. Nevertheless, it should be noted that this study has been performed with a small group and should be replicated in a larger group. In addition, this study has used dichotomous variables, which allowed direct comparison of all anatomy and physiology measures. However, this can limit our understanding of how the strength of measure can influence hand function. Future studies could potentially use continuous variables not just for TMS laterality, but for other variables as well.

Conclusions

The somatosensory findings reinforce the importance of considering the anatomical and functional state of this system in USCP at an early age. Considering previous studies where somatosensory training[43] or peripheral nerve stimulation[44] has indicated promise in improving motor deficits, specifically demonstrated in diplegic CP[45], it might be useful to evaluate the inclusion of such training early on in the rehabilitation of the motor function in children with USCP. This might be especially useful for the sub-group of children who had a larger cortical-subcortical lesion like MCA ; that occurs close to birth ; or who have a disrupted somatosensory physiology or anatomy. Conversely, intensive motor training has shown concurrent improvements in the somatosensory function[46] ; although ; these improvements in movement and sensation were not found to be correlated and somatosensory improvements did not last.

Another promising intervention for the motor rehabilitation in CP ; has been constraint induced movement therapy[47]. In this approach the less-affected hand is constrained to force the use of the more-affected hand. It remains to be tested whether a similar somatosensory constraint may be beneficial depending on how viable the somatosensory connections are from the injured hemisphere. Further, brain stimulation has also been used in CP to alter motor cortex excitability[48,49]. Our results suggest that connectivity, particularly of the somatosensory system, is critical for hand use in these children. Insofar as non-invasive brain stimulation can alter activity of these cortical networks, it could be a useful tool to improve hand function.

In conclusion, this study demonstrates the importance of both sensory and motor connectivity on hand movement and sensation. These associations were compared directly through 2 independent methods: multivariate and clustering analyses, and both demonstrated strong effects of sensory connectivity and more moderate effects of motor connectivity. Lesion type was found to be correlated with hand function as well. These analyses support our main hypothesis and point to somatosensation as a possible critical driver of hand function in children with USCP. A better understanding of these two circuits integral to hand function could offer new approaches to therapy.

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Supplementary Material

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Acknowledgments

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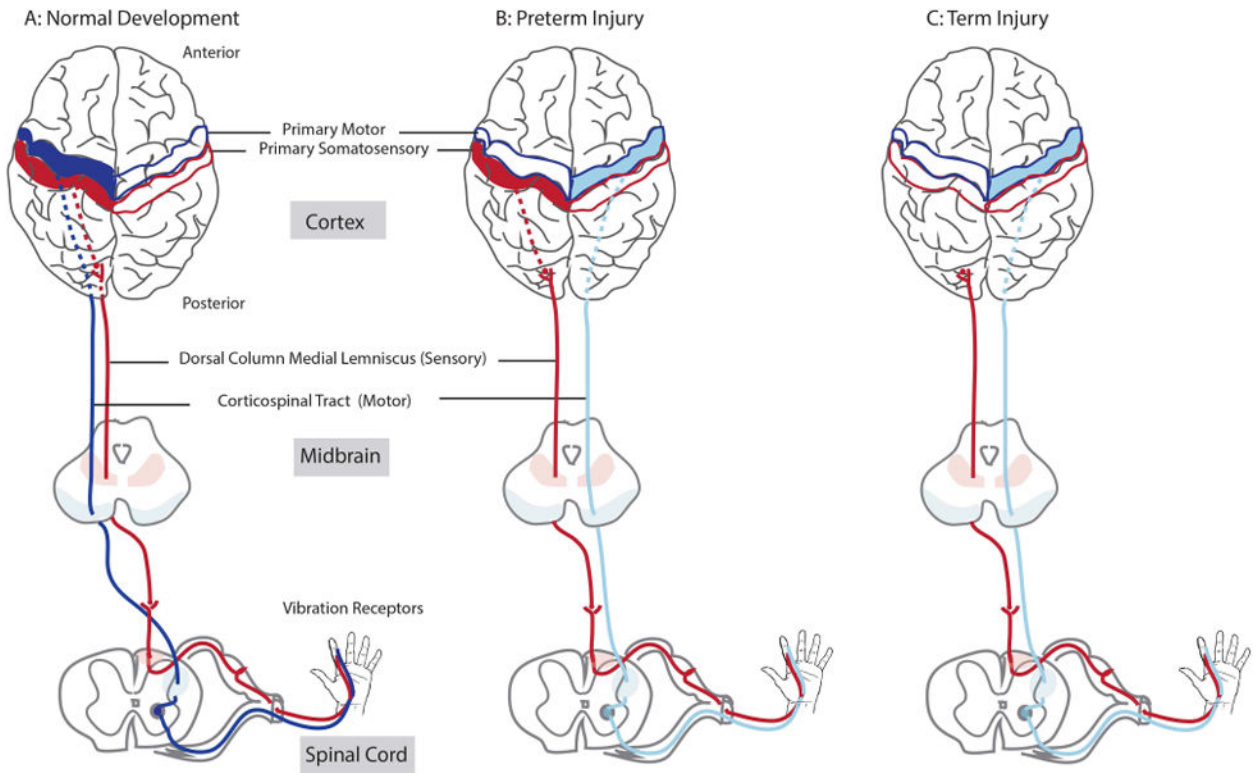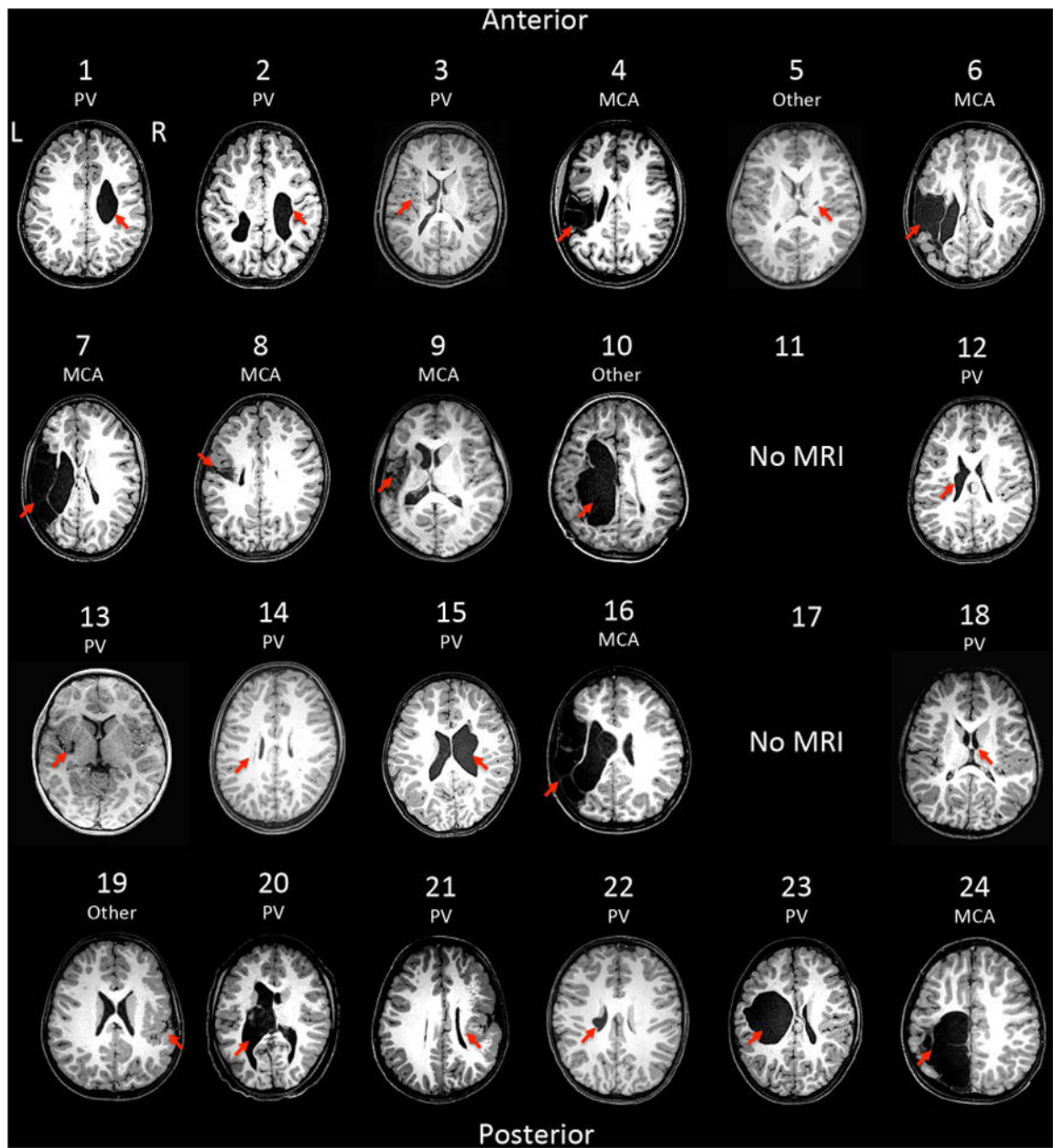
Figure 1.
An illustration of the motor and somatosensory connections in normal development and early brain injury. These are models based on previous studies of the effects of injury timing on connectivity. (A) Typical development. After initial bilateral projections, the motor tract (corticospinal tract (CST), is largely pruned to the contralateral one. The somatosensory tract mediating touch, vibration, and proprioception (dorsal column-medial lemniscus (DC-ML)). (B) In case of preterm injury, the contralateral CST is often disrupted, and the ipsilateral CST persists from the uninjured hemisphere. Thalamocortical projections (interrupted line) that are part of the DC-ML develop later and may skirt periventricular lesions to reach primary somatosensory cortex in the contralateral cortex. (C) In case of a larger injury (such as MCA) that can often occur at full term, the thalamocortical projections and primary somatosensory cortex may be disrupted as well. (Colored version of Figure is available online)
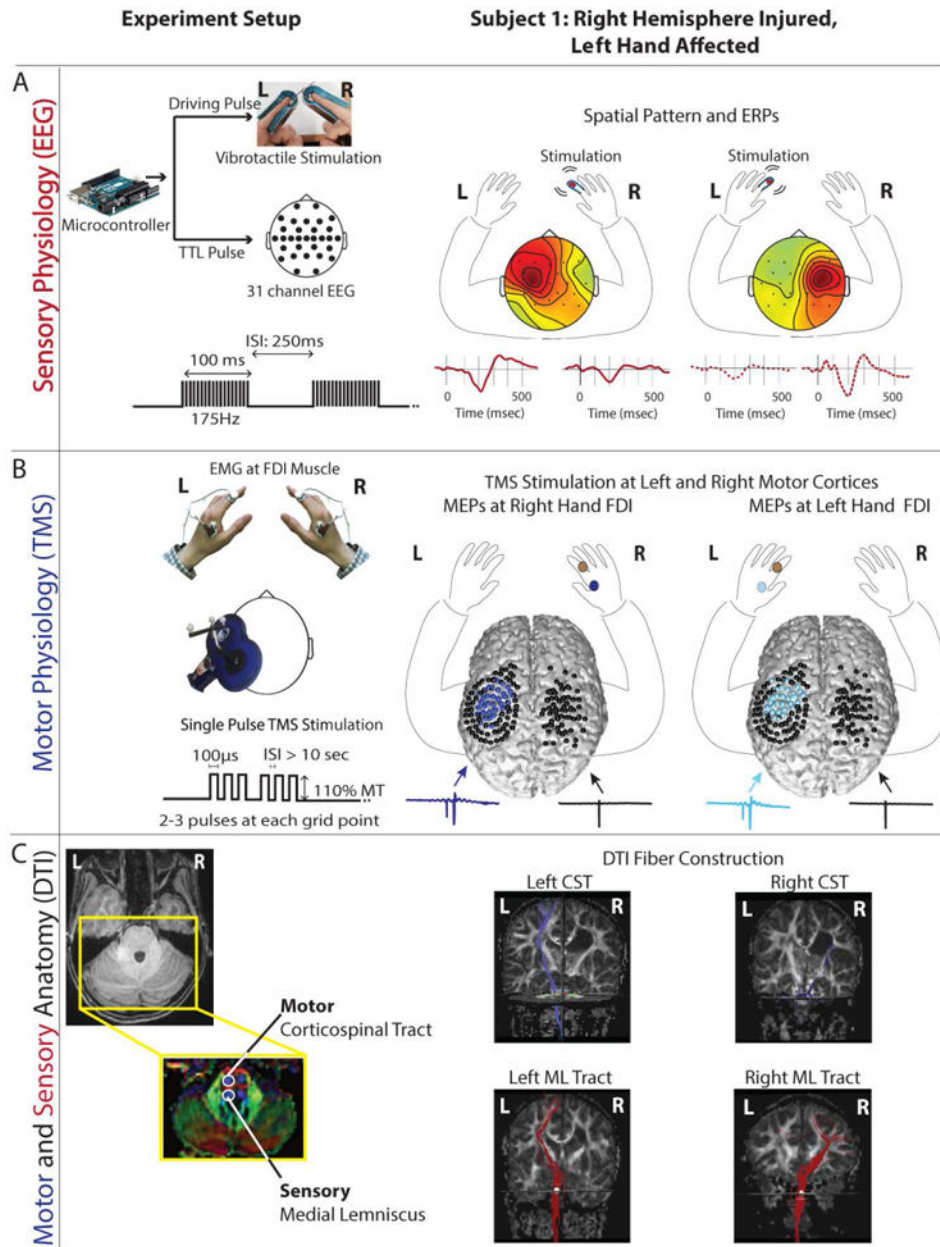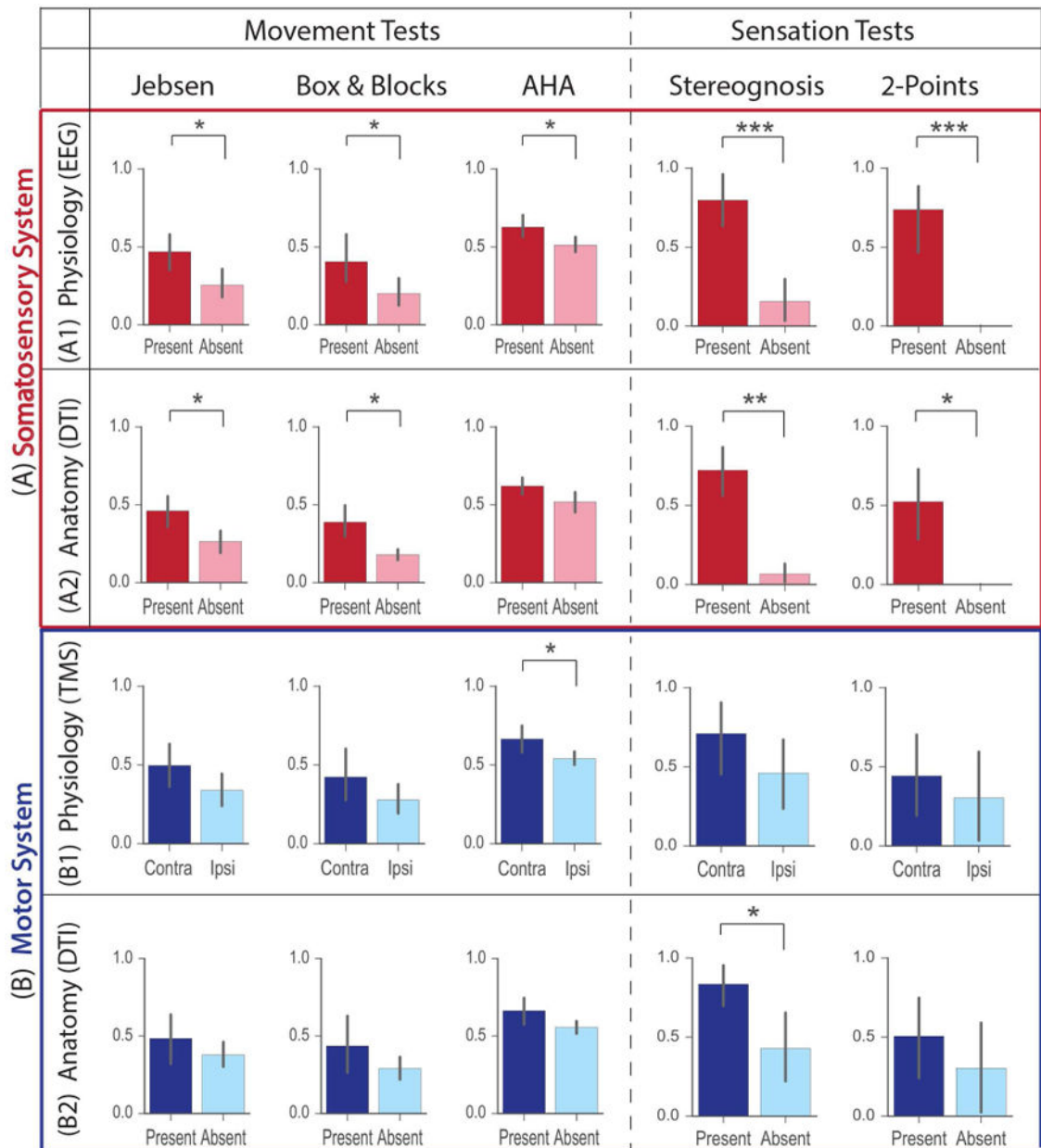
Figure 2.
Experimental methods. The left panel shows the methods for data acquisition for assessment of physiology and anatomy. The right panel shows the results for one example participant with right hemisphere PV injury with preserved somatosensory connections and ipsilateral motor connections. (A) Sensory physiology. Left: EEG SEPs were evoked with vibrotactile stimulation applied to the tip of each index finger. Right panel shows the spatial topographies and SEPs for left and right hand stimulation. Comparable contralateral evoked response is observed for stimulation of both the left (more affected) and right (less affected) hand. (B) Motor Physiology. Left: Single pulse TMS stimulation applied using neuronavigation evoked MEPs in the first dorsal interosseus muscle. Right: black spheres indicate the sites of stimulation projected onto a 3D rendering of the patient's cortex. The

locations that evoked an MEP are shown in dark blue for the contralateral (right) hand and light blue for the ipsilateral (left) hand (same scheme as Fig 1). (C) Anatomy: Left: DTI of the motor and somatosensory tracts displayed on a color-coded DTI FA map. In FA maps the red indicates fibers running along left-right direction, green inferior-superior and blue anterior-posterior. The CST (anterior pair of blue) and medial lemniscus (posterior pair of blue) were seeded on an axial slice at pons level. Right: CST (shown in blue) is found in the left (uninjured) hemisphere, but not in the right hemisphere with the PV lesion. In contrast, the somatosensory tracts (shown in red) are present in both the left and the right hemisphere.

Figure 3.
Structural MRI's for all participants, indicating (shown by arrow) the location and type of the lesion. PV: Periventricular, and MCA: Middle Cerebral Artery.

Figure 4.
Correlation of somatosensory and motor anatomy and physiology with hand function. Movement tests (Jebsen Taylor, Box & Blocks and AHA) are shown in the left panel and sensation tests (Stereognosis and 2-point Discrimination) in the right. (A) Somatosensory Connectivity: The presence or absence of physiological connectivity in injured cortex, as measured with SEPs, was significantly correlated with all movement and sensation tests. The absence of a SEP was associated with poor hand function. The presence or absence of anatomical connections in injured cortex, as seen with DTI was significantly correlated with hand function for all test except AHA. Absence of tracts was associated with poor hand function.

(B) Motor Connectivity: The presence of predominant contralateral or ipsilateral physiological connections, as measured by TMS, was not significantly correlated with most movement and sensation test scores, except AHA. The presence or absence of anatomical connections in injured cortex, as seen in DTI, were not significantly correlated with hand function tests, except Stereognosis. The absence of the crossed CST was associated only with poor stereognosis. Significance was estimated by a non-parametric permutation test: *** = p < 0.001, ** = p < 0.01, * = p < 0.05. (Colored version of Figure is available online)
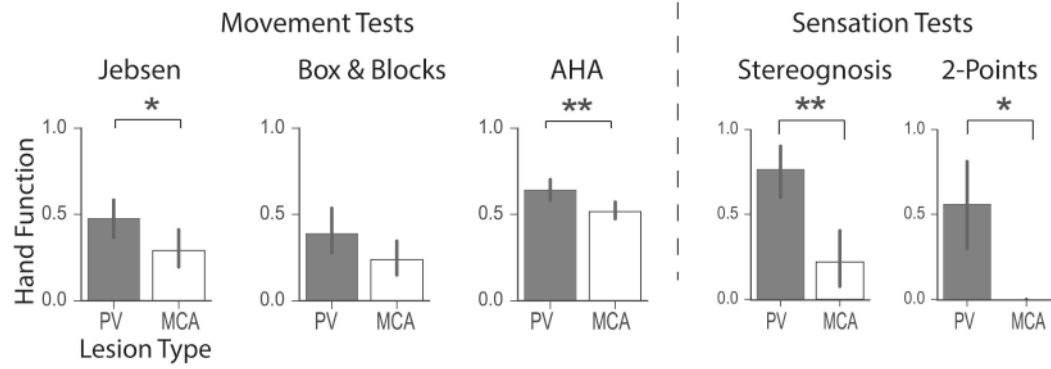
Figure 5.
Correlation of lesion type and sensory and motor function. PV and MCA lesion types are significantly different in their impact on the motor (Jebsen Taylor and AHA) and sensory (Stereognosis and 2-Points) function. PV is generally associated with better hand movement and sensation scores than MCA, except for Box & Blocks. Significance was estimated by a non-parametric permutation test: *** = p < 0.001, ** = p < 0.01, * = p < 0.05.
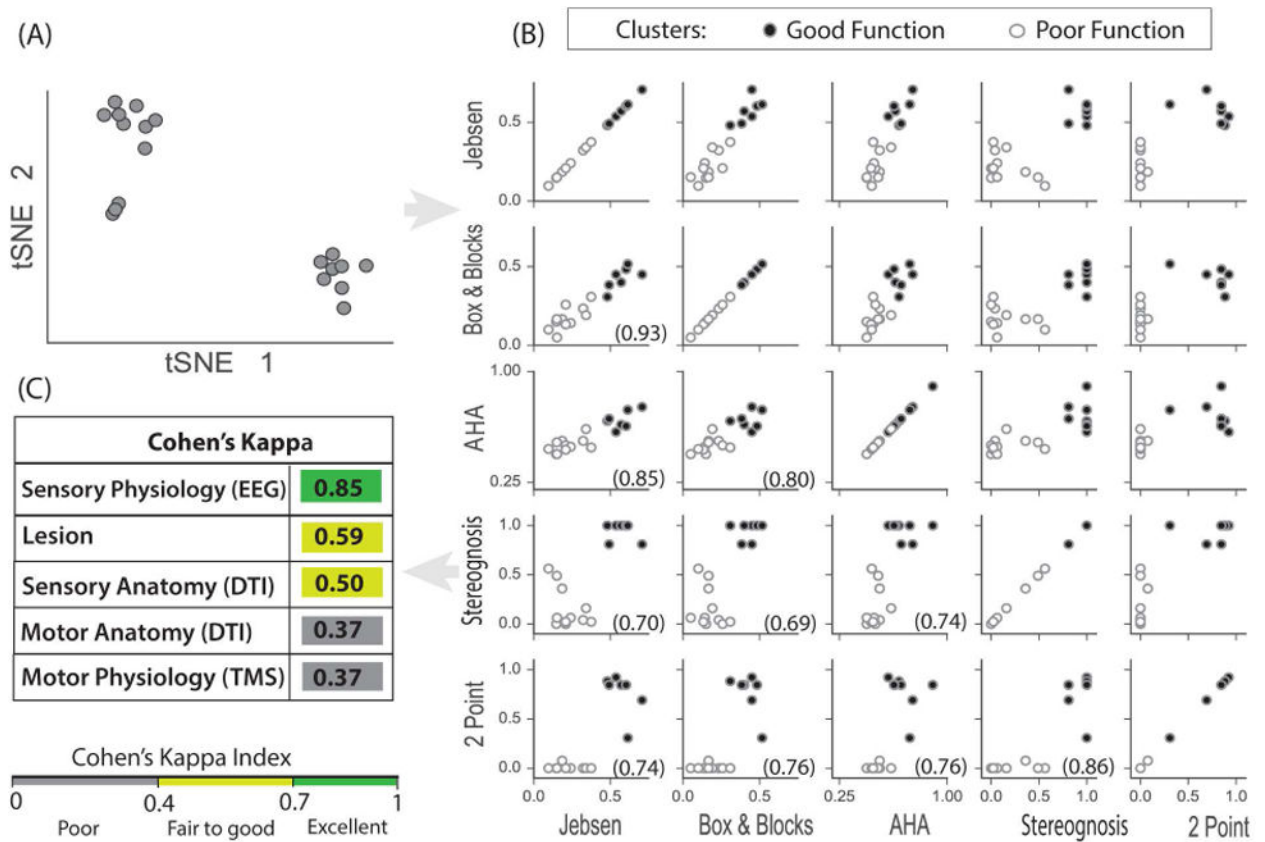
Figure 6.

Clustering of behavioral data. (A) t-SNE allows projections of the 5 hand function tests into 2 dimensions (t-SNE 1 and t-SNE 2) which shows 2 distinct participant groups. (B) Clustering outcome from applying k-means clustering on 5 dimensional hand function data. The two clusters are marked for all pairs of hand movement and somatosensory test scores. Each circle represents a single participant, and circles are filled or open based on the 2 clusters. The clusters fall into the top right quadrant (good hand function: filled circles) and the lower left quadrant (poor hand function: open circles) for all pairs of hand function tests. All tests pairs were also significantly correlated, tested with non-parametric Spearman's rho (p < 0.001), rho is shown in each subplot in parentheses. (C) Cohen's kappa was used to estimate cluster agreement with anatomy, physiology and lesion type. Somatosensory physiology was the most sensitive indicator of good or poor hand function.

Table 1

Participant demographics, injury type and location, physiology and anatomical connectivity

Index: Contra: contralateral; ipsi: ipsilateral; T/P: Technical Problem; I/D: Incomplete Data; N/A: No significant SEP classification in the unaffected hemisphere. *: No TMS Hotspot Found;

Demographics			Injury		Physiology		Anatomy	
P	Age	Sex	Lesion	Cortex	Motor	Sensory	Motor	Sensory
	(y.m)				(TMS)	(EEG)	(DTI)	(DTI)
1	13.06	m	PV	R	Ipsi	Present	Absent	Present
2	8.10	f	PV	R	Ipsi	Present	Absent	Present
3	16.10	f	PV	L	Ipsi	Present	Absent	Present
4	18.12	f	MCA	L	Ipsi	Present	Absent	Present
5	8.01	m	Other	R	Ipsi	Present	Absent	Present
6	9.06	m	MCA	L	Ipsi	Absent	Absent	Absent
7	9.06	f	MCA	L	Ipsi	Absent	Absent	Absent
8	12.03	m	MCA	L	Ipsi	Absent	Absent	Present
9	10.07	m	MCA	L	Ipsi	Absent	Present	Present
10	13.08	f	Other	L	Ipsi	Absent	no DTI	no DTI
11	9.03	m	no MRI	L	Ipsi	Absent	no DTI	no DTI
12	10.01	m	PV	L	Contra	Present	Present	Present
13	10.03	f	PV	L	Contra	Present	Present	Present
14	11.01	m	PV	L	Contra	Present	Present	Present
15	7.08	f	PV	R	Contra	Present	Absent	Present
16	7.02	f	MCA	L	*	Absent	Absent	Absent
17	11.01	m	no MRI	L	Contra	Absent	no DTI	no DTI
18	7.05	f	PV	R	Contra	N/A	Present	Present
19	7.01	m	Other	R	Contra	N/A	Present	Present
20	7.12	f	PV	L	Contra	I/D	no DTI	no DTI
21	12.05	m	PV	R	Contra	T/P	Present	Present
22	13.08	m	PV	L	Ipsi	T/P	Present	Present
23	7.02	f	PV	L	*	Absent	Absent	Absent

Demographics		Injury		Physiology		Anatomy	
				Motor	Sensory	Motor	Sensory
	Age	Sex	Lesion	Cortex	(TMS)	(EEG)	(DTI)	(DTI)
P	(y.m)							
24	8.03	m	MCA	L	*	N/A	Absent	Present

Table 2

A) **Effect sizes:** Cohen's d was used for univariate analysis: small (0.2), medium (0.5), large (0.8), very large (1.3)[50]. Minimum effect size for representing a 'practically' significant effect (d=0.41)[50]. Eta²(η^2) was used for MANOVA: small (0.02), medium (0.13), large (0.26)[50]. Partial eta²(ηp^2)[50] was used in multiple regression: small (0.01-0.06); medium (0.06-0.14); large (>= 0.14).

Significance and effect size for univariate and multivariate statistical analysis

Significance and effect size for physiological and anatomical multiple regression analysis						
A) Significance (p)	JTHHF	Box&Blocks	AHA	Stereo-gnosis	2-Point	MANOVA
Sensory Physiology (EEG)	0.0152	0.0462	0.0176	0.0008	0.0007	0.0003
Sensory Anatomy (DTI)	0.0417	0.0144		0.001	0.028	0.0005
Lesion	0.0426		0.0092	0.0026	0.014	0.0005
Motor Anatomy (DTIm)			0.0186	0.014		
Motor Physiology (TMS)						
Effect Size (d, η^2)	JTHHF	Box&Blocks	AHA	Stereo-gnosis	2-Point	MANOVA
Sensory Physiology (EEG)	1.23	1.02	1.12	2.59	3.21	0.7
Sensory Anatomy (DTIs)	1.03	1.12	0.92	2.34	1.44	0.37
Lesion	1	0.76	1.3	2	1.74	0.42
Motor Anatomy (DTI)	0.53	0.71	1.02	1.21	0.48	0.15
Motor Physiology (TMS)	0.78	0.71	1.19	0.88	0.49	0.12

Significance and effect size for univariate and multivariate statistical analysis

		Box&Blocks	AHA	Stereo-gnosis	2-Point	MANOVA
B1) Model p value		0.033		0.032	0.001	0.001
Model r²		0.408	0.294	0.409	0.633	0.777
EEG	P val	0.031			0.0009	0.0009
	ηp^2	0.308	0.144	0.207	0.5831	0.721
	CI	[−434.2 −23.5]	[−5.0, 23.9]	[−1.7, 20.9]	[2.8, 8.4]	[−13.2, −4.8]
	Coeff	−228.9	9.4	9.6	5.6	−9.0
TMS	P val	0.38	0.22	0.123	0.579	0.379
	ηp^2	0.06	0.122	0.172	0.024	0.087
	CI	[−312.2 127.3]	[−6.6, 26.0]	[−2.9, 21.3]	[−2.2, 3.8]	[−6.2, 2.6]
	Coeff	−92.4	9.7	9.2	0.8	−1.8

Significance and effect size for physiological and anatomical multiple regression analysis

A) Significance (p)	JTHHF	Box&Blocks	AHA	Stereo-gnosis	2-Point	MANOVA
B2) Model p value						
Model r²		0.105	0.22	0.26	0.62	0.31
DTIs	**p value**				**0.001**	**0.047**
	ηp^2	0.101	0.112	0.045	0.479	0.269
	CI	[−436.3 90.6]	[−4.9, 24.9]	[−7.7, 19.2]	[2.4, 7.9]	[−14.1, −0.09]
	Coeff	−172.9	10	5.7	5.2	−7.1
DTIm	**p value**					
	ηp^2	0.005	0.048	0.143	0.136	0.002
	CI	[−186.4 243.8]	[−7.2, 18.0]	[−2.2, 19.8]	[−0.5, 4.0]	[−5.6, 6.6]
	Coeff	28.7	5.4	8.8	1.7	0.5

Note: **B2) Model p value** = **0.0002** (2-Point column).