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Effects of stochastic resonance stimulation on manual function in children with hemiplegic cerebral palsy: A pilot clinical trial

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Abstract

Objective: To investigate the effect of stochastic resonance stimulation (SRS) on manual abilities in children with hemiplegic cerebral palsy.

Design: This pilot study is a randomized, sham-controlled, one-period, cross-over trial.

Setting: A neuroscience clinic with specialty therapy programs at an urban, university-based children's hospital.

Participants: Sixteen children ages 3 to 16 years who were diagnosed with hemiplegic cerebral palsy and had hand Manual Abilities Classification scale score of I to III with sufficient cognitive abilities to follow instructions.

Interventions: Children donned wrist and arm bands that delivered SRS via embedded piezoelectric actuators in two randomly assigned conditions: sham (devices powered off) and subthreshold stimulation (SBT-SRS). Following the randomized protocol, a subset of participants also completed an open-label, above-threshold stimulation (AT-SRS) condition. Children carried out the same uni-manual and bimanual tasks during the randomized and open-label protocols; all data were collected in a single session.

Main Outcome Measure(s): Box and Blocks (B&B) test, a uni-manual function test, and the Shriners Hospital Upper Extremity Evaluation (SHUEE). The SHUEE was video recorded and scored by two raters who were blinded to the experimental condition.

Results: Thirteen children completed the B&B task and 14 children completed the SHUEE. Children in the SBT-SRS condition relative to sham condition moved an average of 1.8 more blocks in 1 minute ($p = .08$); scored an average of 3 points higher on SHUEE spontaneous functional analysis ($p < .002$); and scored an average of 2.7 points higher on SHUEE dynamic positional analysis ($p = .20$). In the open-label protocol, children in the AT-SRS condition relative to sham moved 3.9 more blocks than in the sham condition ($n = 8$, $p < .001$); scored an average of 4.5 points higher on SHUEE spontaneous functional analysis ($n = 6$, $p = .08$); and scored an average of 10.5 points higher on SHUEE dynamic positional analysis ($n = 6$, $p = .01$).

Conclusion(s): In this pilot study, we found preliminary evidence that children with hemiplegic cerebral palsy demonstrated improved uni-manual abilities and increased function of the impaired hand on bimanual tasks when receiving a single session of SBT-SRS. Preliminary evidence also suggests that some children with hemiplegic cerebral palsy may improve more when receiving a single session of AT-SRS. Future research using larger, controlled studies should

evaluate the optimal intensity, duration, and long-term effect of SRS for improving impaired manual abilities.

Cerebral palsy (CP) is the most common neurodevelopmental disorder among children. CP affects between 1.5 and 3 of every 1000 live births in the United States and presents with varying levels of impairment.[1] CP is caused by a nonprogressive neurological lesion to the developing brain in utero or during infancy. The lesion affects the development of movement, muscle tone, and posture and can co-occur with deficits in sensory perception as well as other developmental disabilities.[2] Upper extremity (UE) dysfunction and the resulting impact on functional independence experienced by individuals with CP can lead to pain, depression, social isolation, increased medical costs, and decreased access to education and vocational pursuits.[3]

Throughout development, movement is continuously refined through reciprocal interactions between the visual and somatosensory systems and the motor cortex.[4] Typical UE motor development begins in utero with spontaneous movements that allow the fetus to explore its own body.[5] In the neonate, movements remain primitive and often reflexive in nature. Reach toward objects begins to emerge at around 4 months of age, although motor control lacks accuracy and is not yet adapted to the properties of the object. Touch begins to inform grasp at around 7 to 8 months of age.[6] As an infant approaches the first year of life, tactile information becomes more successfully integrated with visual input.[7] Sensory signals provide feedback to the central nervous system to refine motor control during reach and prehension, as well as through a feedforward mechanism, which contributes to anticipatory control and motor planning.[5,7]

Children with CP also often demonstrate impaired somatosensory function. Compared with typically developing children, children with CP have impaired texture perception,[8] stereognosis (shape perception),[2,8,9] two-point discrimination, tactile registration of a monofilament,[2,10-12] perception of direction of a tactile stimulus, proprioception,[13-15] kinesthesia,[16] and reduced sensory evoked potentials in response to tactile cues.[2,15] Seventy-five percent of children with unilateral CP experience tactile deficits, with over 40% experiencing deficits in both tactile registration and perception.[17,18] Impairments in tactile registration and/or in tactile perception at the cortical level[17] may have strong implications for higher-level processing such as development of visual-spatial skills, sensory integration, and bilateral coordination, among other skills necessary for daily functional performance.

Mainstream rehabilitative interventions have focused primarily on improved movement and function through the reduction of motor impairments such as spasticity, weakness, and contracture.[17] If the motor impairment is partly due to deficits in sensory processing, then interventions that augment sensory function may have a therapeutic effect to improve motor performance.[7,17] Orthoses designed to influence the sensory system, including sensory motor foot orthoses[19] and compression garments,[20,21] have demonstrated large effects in improving movement in persons with CP; however, motor impairments remain substantial, highlighting the need to establish additional sensory-based interventions to improve motor performance in CP.[7,17]

Stochastic resonance stimulation (SRS) can improve sensory function and integration in humans.[22] SRS can be defined as a nonlinear phenomenon whereby the addition of a random interference, ‘‘noise’’, can enhance the neuronal processing of sensory stimuli. SRS applied to peripheral sensory neurons directly increases their firing rate in response to poorly detectable stimuli,[23,24] and enriches the information content of afferent signals to the central nervous system (CNS).[22,25,26] SRS to peripheral sense organs can support enhanced cortical processing of stimuli.[27] In humans, SRS applied at an optimal level, below a person’s threshold, enabled more sensitive and accurate detection of tactile stimulation in the fingertips[26,28] and plantar surfaces.[29-32] While augmenting sensory perception, application of SRS to the hand improved manual dexterity in fine motor tasks in typical individuals.[33] Application of SRS to the lower extremity has been shown to reduce sway parameters and improve balance in elderly persons at high risk for falls,[34,35] increase functional agility in athletes,[36] as well as enhance standing balance in individuals with CP.[11,37]

In multiple uncontrolled trials conducted in our clinics, we observed improved speed and accuracy of reach and manipulation in children performing manual tasks while wearing SRS applied to the wrist and upper arm. In some of these trials, children appeared to have a greater clinical response when receiving stimulation above their detection threshold. The majority of studies focus on the effect of SRS on a single sensory modality, and support the use of subthreshold noise to optimize signal detection; however, in the context of multiple sensory pathways working in parallel, application of above-threshold noise may result in optimal signal processing.[38,39]

To assess whether SRS applied to the upper arm could improve UE function in children with CP, we initiated this pilot clinical trial. Our primary aim was to use lightweight wearable SRS devices (Accelera[i]), consisting of wraps that contain a battery-powered piezoelectric actuator, to deliver vibro-tactile noise and

FIGURE 1 Schematic of study flow describing progression from recruitment, consent process, assessment of patient characteristics and stochastic resonance stimulation (SRS) detection threshold, and completion of outcome measures. 2PD, two point discrimination; B&B, box and blocks test; CHOR-VCU, Children's Hospital of Richmond at Virginia Commonwealth University Health Systems; MACS, manual abilities classification scale; SHUEE, Shriners Hospital Upper Extremity Evaluation; TASC, test of arm selective control

compare performance in two treatment conditions: sham (device powered off) and subthreshold stimulation (SBT-SRS). We hypothesized that receiving SBT-SRS would improve manual dexterity and functional performance compared to the sham control condition. Our secondary aim was to evaluate the effects of above-threshold stimulation (AT-SRS) on manual function (Figure 1).

METHODS

Study design

This pilot study is a randomized, sham-controlled, one-period, crossover trial. To the extent possible, participants and raters were blinded to the sham and SBT-SRS conditions. This design allowed us to conduct the two primary experimental conditions during a single clinic visit. The single session was conducted at an outpatient therapy center or physical medicine and rehabilitation clinic, which are part of an urban, university-based, children's medical center of care. The order of studies in the sham condition or the treatment condition was varied randomly to minimize the effect of practice. Participants could not be blinded to the AT-SRS experimental condition, and it was conducted open-label after the randomized-controlled protocol. The Shriners Hospital Upper Extremity Evaluation (SHUEE) was video recorded and scored by two raters who were blinded to the randomized-controlled and open-label experimental conditions to reduce rater bias.

Participants

Recruitment occurred during the period from July 15 to November 15, 2020. Recruitment ended when sponsor funding expired. Participants were recruited through the following sources: (1) attending physicians at Children's Hospital of Richmond at Virginia Commonwealth University Health Systems (CHOR-VCUHS), (2) study divulgation though the neurosciences services at CHOR-VCUHS, and (3) flyers posted in outpatient and pediatric neurosciences clinics. Inclusion criteria were: (1) diagnosis of hemiplegic CP; (2) 3 to 18 years of age; (3) able to reliably express pain, discomfort, or fear as reported by parent/guardian; and (4) Manual Ability Classification Scale (MACS) levels I, II, or III.[40] Participants were excluded from participation if they had aggressive behavior, cognitive deficits, developmental limitations that precluded following the study protocol instructions, or a history of botulinum toxin injection within the previous 6 months. The study protocol and consent forms were approved by the university's institutional review board (IRB) protocol #HM20018459. The study procedures were described, and the equipment was shown to the participants and their parents/guardians. All study procedures and associated risks were explained. Enrollment was initiated when the parents/guardian thoroughly understood and signed the consent form, and, when appropriate, the child participant provided assent. No study interventions were initiated, or no measures were collected, until signed consent was provided. Participants and family members were screened for signs and symptoms of coronavirus disease 2019 (COVID-19) infection. Participants and staff adhered to social distancing, to the extent possible, and mask wearing and strict hand hygiene throughout the study procedures.

Participant characteristics

The following clinical assessments were performed before initiation of study conditions by a single interventionist: (1) Modified Ashworth Scale (MAS) to evaluate the severity of spasticity on a scale of 0 to 4 at the shoulder, elbow, wrist, and fingers and expressed as an average score for all the movements tested[41]; (2) Test of Arm Selective Control (TASC)[42]; and (3) assessment of tactile registration of monofilament and two-point discrimination testing on the pad of the index finger.[43,44] Tactile registration was scored as the lightest weight monofilament that a participant could accurately detect on at least two of three touches. Two-point discrimination distance was determined by the minimum distance between two tips of a caliper that could be distinguished from a single point stimulation accurately on at least four of five touches.

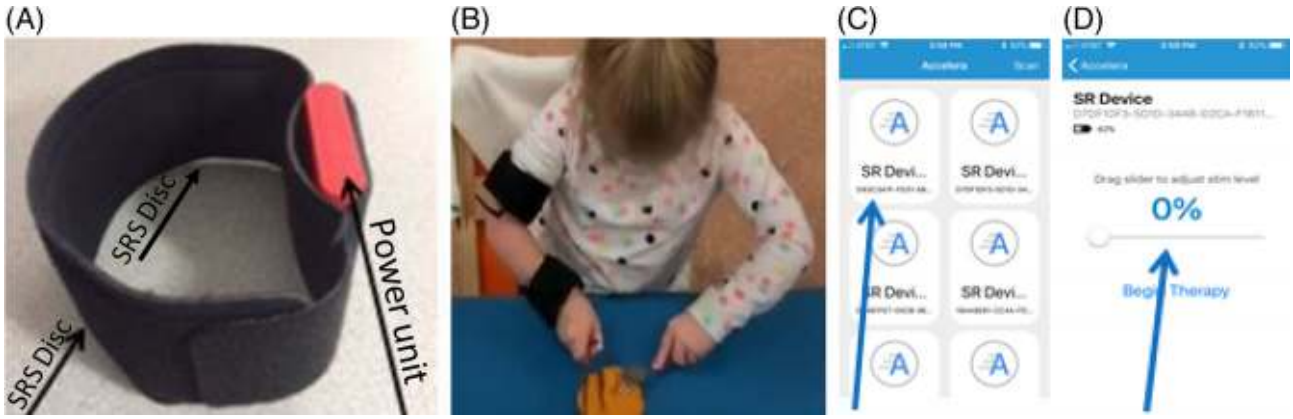

FIGURE 2 (A) Picture of the stochastic resonance stimulation (SRS) device. The power unit is contained in a small pocket and is connected to two actuator discs sewn into a Neoprene sleeve. (B) A participant wearing the wraps around the upper arm and wrist. (C) Screen shot from an iPhone showing multiple connected devices that can be selected and adjusted individually. (D) Image of scroll bar for adjusting SRS amplitude from 0% to 100% of max device amplitude

Measures

Primary outcomes

We used validated measures of manual ability in CP, the Box and Blocks test (B&B),[45,46] and SHUEE[47] to quantify changes in UE function in children with CP treated with SRS. The B&B is a test of gross manual dexterity that is commonly used to assess function of the affected versus the nonaffected hand in individuals with unilateral CP. The test measures the speed of lifting, carrying, and releasing blocks within a 60-second period. Concurrent validity with the Movement Assessment Battery for Children-2 (MABC-2) is moderate but significant.[45] The SHUEE is used to assess UE bimanual functioning in children (ages 3 to 18 years old) with unilateral CP. The SHUEE consists of 16 bimanual tasks graded in two domains: Spontaneous Functional Analysis (SFA) and Dynamic Positional Analysis (DPA). SFA measures the child's ability to spontaneously use the affected UE during specified tasks and DPA assesses segmental analysis of the UE during these tasks. A third domain, Grasp/Release Analysis (GRA), assesses the ability to grasp and release an object with the wrist positioned in extension, flexion, and neutral. The SHUEE shows acceptable correlation ($r = 0.47$) with the Pediatric Evaluation of Disability Inventory (PEDI)[47] and has been used previously as an outcome measure for UE function in hemiplegic CP.[48]

Study procedure

SRS actuators, contained within a Neoprene wrap, were applied to the ventral and dorsal surfaces of the wrist as well as at the upper arm on the tested (affected) side. The actuators within the wrap vibrate with a random peak to peak frequency between 10 and 325 Hz, with a maximum displacement amplitude of ~50 μm. The devices are powered on via an iPhone app, and the stimulus intensity can be adjusted by increments of 1% from 0% to 100% of maximum stimulus amplitude. Each participant's threshold for detection of SRS was determined by the study staff prior to initiating the testing condition. The detection threshold was determined using the method of ascending and descending limits, where the intensity of noise was increased and decreased until the participant was unable to distinguish between it being on or off.[49] Detection thresholds for the wrist and the upper arm were established separately. The detection threshold value for each participant was not recorded as an outcome. In prior studies, optimal effects are typically observed when SRS is applied between 75% and 90% of the detection threshold.[26,30,31,50-52] Outcome measures were recorded in each of the following conditions: (1) Sub-Threshold: Target stimulation intensity for SRS applied subthreshold (SBT-SRS) was 90% but in actuality ranged from 80% to 90% of detection threshold; (2) Sham: Participant wearing SRS devices, but devices not turned on; and (3) Above Threshold SRS (AT-SRS): target intensity was 110% of detection threshold, but ranged from 110% to 120% of detection threshold. Stimulus intensity is described as a range, because in some cases exactly 90% or 110% of threshold could not be achieved. For example, a participant who had a detection threshold of 12% of device max was provided a stimulus of 10%, that is, 83% of threshold (Figure 2).

Following a pre-assessment, and after the SRS detection threshold was determined, participants completed the two outcome measures in sequence in the same treatment condition. Whether the SBT-SRS

treatment or sham condition was tested first was decided using a coin flip by a study staff member to determine the order of administration. Participants would then perform the B&B and SHUEE consecutively in the same condition (ie, sham or SBT-SRS). After a 5-minute break, participants would perform a second round of outcomes in the alternate condition. Another break was given before repeating the tests in the AT condition. Each iteration of the B&B + SHUEE required ~15 minutes. Participants younger than 6 years of age struggled with some of the procedures in the pre-assessment and the outcome measures. When participants showed signs of frustration or refusal, we prioritized completion of the outcome measures before obtaining all patient characteristics. Some struggled with having to use their impaired hand exclusively for the B&B task; others had difficulty following the instructions of the SHUEE. If frustration or inability to follow instruction was noted, the interventionist would move on to the next outcome.

Per protocol, participants and assessors were blinded to the SBT-SRS treatment and sham condition assignments. Because the devices emit an audible noise at higher settings, or because participants could use the more-sensitive tactile function of their contralateral finger pads, there was the potential for participants to determine when devices were powered on. During study sessions, one staff member operated the devices, and a second blinded interventionist kept time during the B&B test, counted the number of blocks transferred, and prompted the participant through the study tasks.

Video recordings were collected during the visit while the participants performed the SHUEE. Videos were reviewed and scored independently by a licensed and registered occupational therapist and a physiatry resident who were blinded to all test conditions (sham, SBT, and AT). Video reviewers were instructed to view the participants' video-recorded performance on tests without audio to reduce the risk of guessing the participants' treatment condition assignment. The average of the two independently rated scores were used for data analysis. On 9 of the 68 trials scored, the difference was greater than 10%. When rater scores diverged by more than 10%, reviewers were notified of their discrepant scores and asked to review the videos and resubmit new scores.

Statistical analysis

Data analyses were conducted using standard statistical methods for randomized clinical trials. All statistical assumptions—normality, homogeneity of variances, linearity, and independence—were tested using descriptive statistics and graphical displays. No statistical transformations of outcome data were required. Because this study used a crossover research design, all participants served as their own control so there were no differences in treatment conditions at baseline. Participants who could no longer follow the study procedures or withdrew from the single period study midstream had a subset of outcome assessments completed. All completed outcome assessments were used in the data analyses. Where a measure was not administered, the assessment was treated as missing. For all efficacy variables, analyses were conducted at $p \leq .05$, for an overall type I error of $\alpha = 0.05$ (two-sided test). Cohen's *d* was computed to generate effect sizes.

For the randomized clinical trial, repeated-measures, one-way analysis of variance (ANOVA) was used to compare outcomes for the sham and SBT-SRS conditions on the B&B and SHUEE measures. In the open-label trial, one-way ANOVA was also used to compare performance on the B&B and SHUEE test in the AT-SRS and sham conditions.

To identify potential patient characteristics associated with a positive response to SRS therapy, Spearman rank correlation analyses were conducted to evaluate the correlation between change in outcome score in response to treatment (SBT-SRS only) and baseline measures of age, MAS score, and TASC score. Correlation analysis was not performed for tactile registration and two-point discrimination scores due to the small sample size. Given the small sample size, no adjustments for baseline characteristics could be included in the efficacy analyses.

RESULTS

Participants

Sixteen participants were recruited for the study (mean = 8.8 years; range = 3 to 16 years). For the randomized protocol, we prioritized completion of two iterations of the B&B and two iterations of the SHUEE due to the risk of attention span limitations and behavioral regulation affecting full protocol completion. Twelve participants, 11 of whom were age 8 to 16, completed the randomized protocol. Participants 6 years old or younger had difficulty completing all of the study procedures: one participant who was 3 years of age was unable to complete any of the study procedures, one participant age 6 completed only the B&B tests, and two participants ages 3 and 5 completed only the SHUEE (see Table 1). Four of our participants (1, 5, 6, & 12) were able to determine when they were receiving SBT stimulation.

Subthreshold SRS randomized trial

On average, participants in the "SRS on" condition compared with the sham condition showed a trend in transferring more blocks (B&B test) in 1 minute (mean = 1.8, $p = .08$, $d = 0.25$). The SHUEE SFA

TABLE 1 Study participant characteristics

Study no.	Age (y)	Gender	Laterality	First Trial	MACS	Ashworth	2PD (mm)	Monofilament (g)	TASC
1	10	M	L	Sham	2	1.8	3	NR	8
2	10	M	R	SBT-SRS	2	0.8	4	3.22	9
3	3	M	R	NA	2	–	–	–	–
4	5	M	R	Sham	2	0.8	–	3.61	5
5	9	M	R	Sham	2	1.5	10	2.44	8
6	14	F	L	SBT-SRS	3	2.7	4	2.44	4
7	8	M	R	Sham	1	0.8	–	2.44	10
8	3	M	R	SBT-SRS	3	–	–		–
9	8	F	L	Sham	3	1.3	–	–	7
10	4	F	R	Sham	1	0.5	–	–	12
11	5	M	R	Sham	3	–	–	–	–
12	8	M	L	Sham	2	1.5	3	1.65	6
13	15	M	R	SBT-SRS	2	0.8	–	–	7
14	11	F	L	SBT-SRS	3	1	–	–	6
15	16	M	L	SBT-SRS	3	1.5	–	–	–
16	6	M	R	Sham	2	1.3	–	–	–

Abbreviations: 2PD, two point discrimination; MACS, manual abilities classification scale; SBT-SRS, subthreshold stochastic resonance stimulation; TASC, test of arm selective control.

TABLE 2 Key outcomes by intervention condition

	Box and Blocks			SHUEE-SFA			SHUEE-DPA		
Study no.	Sham	SBT-SRS	AT-SRS	Sham	SBT-SRS	AT-SRS	Sham	SBT-SRS	AT-SRS
1	22	23	28	32	35	–	43	49	–
2	14	19	19	33	37	38	61	60	67
3	–	–	–	–	–	–	–	–	–
4	16	19	–	23	28	–	36	45	–
5	12	12	17	24	24	25	30	18	47
6	9	10	9	27	24	25	27	22	27
7	15	19	20	30	35	34	40	46	53
8	–	–	–	13	14	–	28	31	–
9	3	4	8	16	23	29	27	40	43
10	11	14	13	28	35	34	44	51	55
11	–	–	–	11	16	–	35	31	–
12	0	8	–	14	18	–	32	31	–
13	24	18	–	25	27	–	30	44	–
14	4	5	–	12	13	–	32	40	–
15	5	4	8	9	10	–	17	12	–
16	4	7	8	–	–	–	–	–	–

Abbreviations: AT-SRS, above threshold stochastic resonance stimulation; DPA, Dynamic Positional Analysis; SBT-SRS, subthreshold stochastic resonance stimulation; SHUEE, Shriners Hospital Upper Extremity Evaluation; SFA, Spontaneous Functional Analysis.

scores of participants in the "SRS on" condition increased a mean of 3 points ($p = .002$, $d = 0.34$, see Figure 1B) whereas DPA mean score increased 2.7 points, but was not significant ($p = .20$, $d = 0.22$, see Figure 1C). Eleven of 14 participants scored 100% on the GRA in the sham condition and did not change in SBT. Two participants scored 4 of 6 in GRA in both sham and SRS conditions and another scored 5 of 6 in all conditions.

Above-threshold, open-label trial

A subset of nine participants completed at least one measure in the open-label trial using stimulation at 110% to 120% of threshold (Table 2). In this condition, participants ($n = 9$) improved by a mean of 3.9 blocks transferred ($p < .001$, $d = 0.52$). On the SHUEE-SFA and SHUEE-DPA tasks, participants improved by a

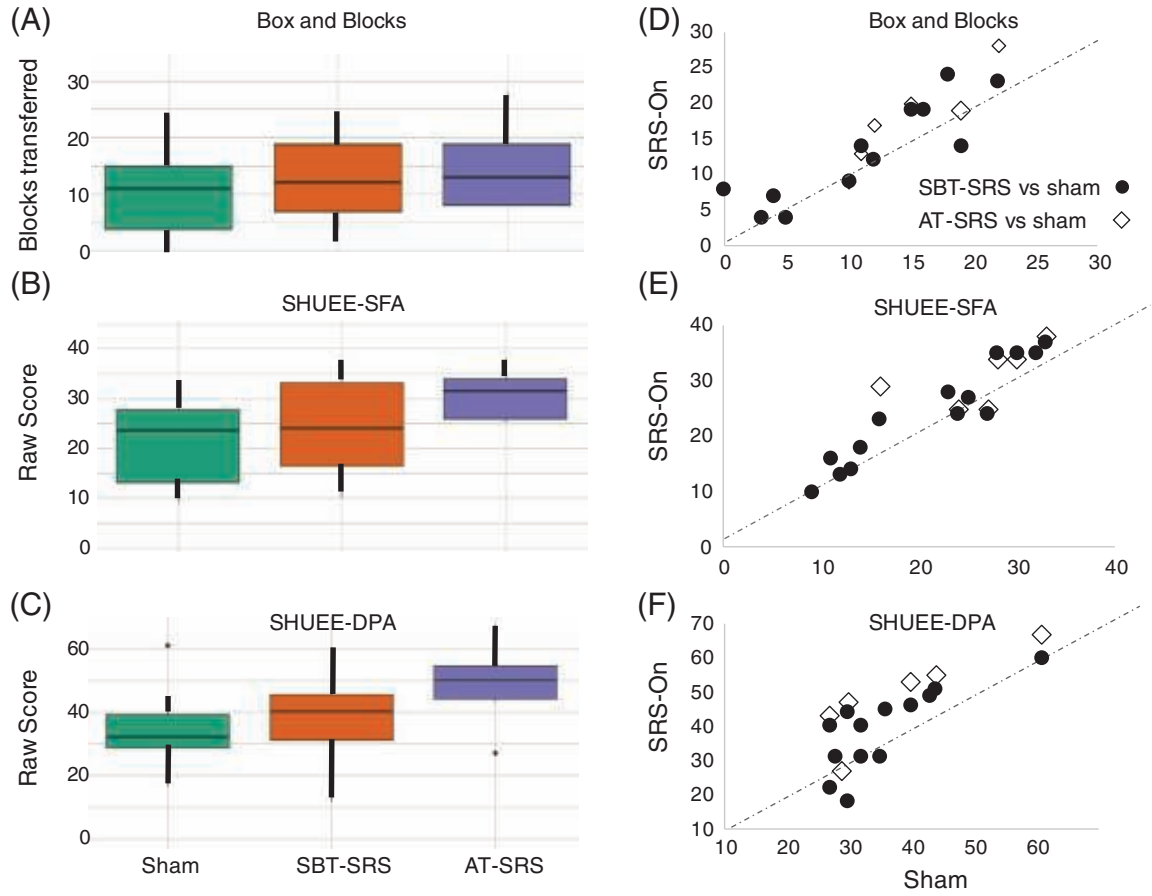

FIGURE 3 Mean and interquartile range of participant raw scores for the (A) Box and blocks test (B) Shriners Hospital Upper Extremity Evaluation (SHUEE)-SFA (Spontaneous Functional Analysis) and (C) SHUEE-DPA (Dynamic Positional Analysis) under three different conditions: sham (green bars) subthreshold stimulation (orange), and above threshold (purple). Comparison of performance of under sham condition (x-axis) and treatment condition for each individual participant (y-axis) for (D) Box and Blocks (B&B) test, (E) SHUEE-SFA, and (F) SHUEE-DPA. Filled circles represent comparison of sham with subthreshold SRS; open diamonds compare sham with above threshold SRS. Dashed line represents identity line where sham = treatment. Points above the line represent improved outcome with treatment

mean of 4.5 points ($p = .08$, effect size 1.25) and 10.5 points ($p = .01$, $d = 1.26$), respectively (Figure 1C). All participants scored 100% on the GRA portion of the SHUEE in both the sham and AT conditions (Figure 3).

Potential patient modifiers of treatment effects

Age had a moderate correlation[53] with ΔSFA ($r_s = 0.66$ $p = .005$), as well as ΔB&B ($r_s = 0.66$, $p = .007$), with younger participants demonstrating greater improvement. With regard to spasticity severity, there was a fair and nonsignificant correlation between the composite MAS score and improvement in SFA in the SBT treatment condition versus sham (ΔSFA), ($r_s = 0.43$, $p = .10$). A moderate and significant correlation existed between MAS score and improvement in DPA in the SBT treatment condition versus sham (ΔDPA), ($r_s = 0.56$, $p = .04$). Participants with lower spasticity scores demonstrated greater improvement on both tests. TASC had poor and not significant correlation with ΔB&B ($r_s = 0.21$, $p = .42$), moderate but not significant correlation with (ΔSFA) ($r_s = 0.44$, $p = .10$), and no correlation with (ΔDPA) ($r_s = -0.06$, $p = .47$) (Figure 4). Due to the small sample of participants completing tactile registration (6) and two-point discrimination assessments (5), we did not report on the correlation of these characteristics with response to SRS therapy (Table 3).

Harms: There were no adverse events recorded. When vibration was brought above threshold, participants were sometimes startled but never expressed any irritation. No participant asked to discontinue the study due to discomfort from the stimulation. The wraps were easy to don and doff, and post-test skin assessment did not demonstrate pressure marks. Many participants and their parents/guardians were disappointed to have to return the devices after the study was completed.

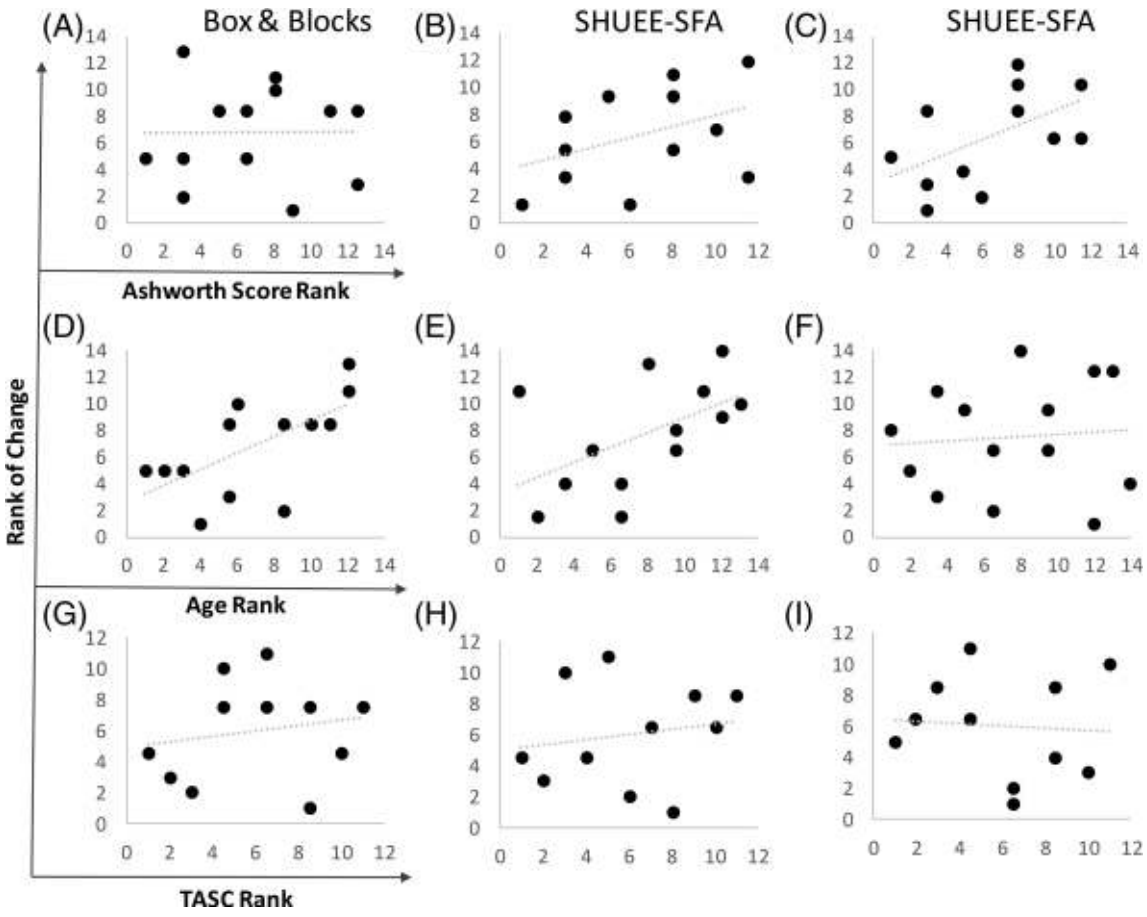

FIGURE 4 Pearson rank correlation plots for change improvement in performance on box and blocks (A, D, G) Shriners Hospital Upper Extremity Evaluation Spontaneous Functional Analysis (SHUEE-SFA) (B, E, H) and SHUEE-DPA (Dynamic Positional Analysis) (C, F, I). Rank is organized from most positive change being ranked 1 and least positive receiving the highest number. For rank of Ashworth, rank of 1 is assigned to the participant with the least spasticity. For age, rank of 1 is assigned to the youngest participant. For Test of Arm Selective Control (TASC), rank of 1 is assigned to highest TASC score

TABLE 3 Rank correlation of participant characteristics and outcomes

	Box and Blocks			SHUEE- SFA			SHUEE- DPA	
	N	r_s	*p*	*N*	r_s	*p*	r_s	*p*
Ashworth	13	−0.15	.33	14	0.43	.10	0.56	*.04*
TASC	11	0.21	.42	11	0.44	.10	−0.06	.47
Age	13	0.66	*.005*	14	0.66	*.007*	0.23	.24

Abbreviations: DPA, Dynamic Positional Analysis; SFA, Spontaneous Functional Analysis; SHUEE, Shriners Hospital Upper Extremity Evaluation; TASC, Test of Arm Selective Control.

DISCUSSION

This study evaluated whether children with hemiplegic or asymmetric CP could show improved UE performance while receiving SRS stimulation of the impaired UE. Our preliminary evidence showed encouraging findings for children with hemiplegic, or asymmetric CP, improving in three distinct aspects of manual abilities when receiving SRS: (1) the ability to produce effort, measured by SFA; (2) joint alignment when performing tasks, measured by DPA; and (3) speed measured by B&B. When receiving SRS during the SHUEE, participants demonstrated increased SFA of the impaired extremity, and some participants also demonstrated substantial improvements in DPA. Change in DPA score was not statistically significant for the whole group in the SBT-SRS condition; however, a subset of children who performed the SHUEE a third time with AT-SRS demonstrated significantly improved DPA. Improvement on the SFA and DPA portions of the SHUEE was inversely correlated with the degree of spasticity. Improved SHUEE-SFA and B&B scores

were inversely correlated with age. Performance on the B&B test improved with SBT and showed greater improvement with AT stimulation.

Greater improvement in the AT condition diverges from prior studies that report optimal effects of SRS with noise input ranging from 70% to 90% of the detection threshold.[26,35] Our AT stimulation ranged from 110% to 120% of threshold. Although this level is not typically considered optimal, SRS slightly above threshold still improves tactile sensitivity relative to baseline.[22] Improved performance in the AT condition may have been due to practice effects, since AT-SRS was always presented as a third condition, whereas SBT-SRS and sham were randomly presented as either the first or second condition. Practice effects were less likely for the B&B test because participants were allowed ample opportunity to practice prior to starting the study assessments. Potentially, a stimulus that exceeds the detection threshold for vibro-tactile receptors on the skin remains below the detection threshold for deeper proprioceptive receptors in the tendons and joints crossing the wrist and elbow. Prior studies that established optimal SRS levels used tactile discrimination, or the firing rate of a single neuron, as the key outcome measure; however, the motor function, as assessed by our outcomes, may be shaped by multiple sensory pathways working in parallel, a circumstance for which application of above threshold noise may be of greater benefit than subthreshold noise signal.[38,39] Our findings of further improvement with AT-SRS warrants further investigation in the optimization of this device to achieve maximum therapeutic benefit for individual users.

The change in SHUEE in our single session trial was comparable to score changes reported after 1 month of constraint-induced movement therapy (CIMT),[48] the gold standard therapeutic treatment for hemiparesis.[54] Children with CP receiving 1 month of CIMT showed improvement in SFA and DPA scores of 15.3% and 7.9%, respectively.[48] In our study, SFA and DPA scores improved by an average 14.1% and 7.9%, respectively, while receiving SBT-SRS, and by 17.1% and 27.5%, respectively, while receiving AT-SRS. The improvement on the B&B was comparatively modest. Compared with sham, participants moved an average of 1.8 more blocks per minute in the SBT-SRS condition and 3.9 blocks in the AT-SRS. Although statistically significant, the increased score in the AT-SRS condition is less than smallest real difference (SRD) reported for the B&B in hemiparetic patients with stroke of 5.5 blocks.[55] Other studies report increases of 4 to 5 blocks per minute in stroke survivors following intensive CIMT interventions.[56,57] The baseline mean for blocks transferred in the study that established SDR was 29 blocks per minute, substantially greater than the baseline values of 10.7 and 14.4 blocks per minute for participants completing SBT-SRS and AT-SRS trials, respectively. Six of 13 participants receiving SBT-SRS, and 7 of 9 participants receiving AT-SRS, had score increases of 3 blocks or more. Given the low baseline function for many of our participants, a change of 3 blocks per minute, although less than the reported SRD, may reflect a modest but significant functional change.

The increase in spontaneous function with SRS may have multiple clinically meaningful implications. First, a significant proportion of the functional impairment in a hemiparetic arm is linked to disuse.[54] As children with hemiplegia often accomplish tasks almost entirely with their less-affected hand, functional asymmetry can increase over the course of development due to the relative lack of engagement of the paretic arm. While wearing the SRS participants were able to generate more effective effort and accomplish tasks more easily with their affected extremity. Therefore, if SRS can help increase spontaneous use of the impaired extremity, it may support functional development with sustained use. Second, participants with spasticity of the affected extremity often demonstrated excess flexion and/or pronation of the UE. Improved dynamic positioning and range of motion while receiving SRS in functional activities may help children with CP develop a greater scope and variability of movements.

Prior studies of SRS applied for UE function showed mixed results. While receiving SRS stimulation to the hand, stroke survivors demonstrated increased tactile sensitivity to monofilament stimulation.[28] In healthy volunteers, SRS applied to the dorsum of the fingertip improved sensory perception and grip force regulation compared to baseline.[33] Another study of stroke survivors assessed the effects of SRS as an adjunct to therapy. In this study, participants received SRS therapy throughout 12 occupational therapy sessions of 1 hour over 4 weeks. Using SRS as a therapy adjunct did not result in greater improvement than a control group receiving occupational therapy alone. Outcomes were tested after treatment with participants not receiving SRS.[58]

SRS technology represents a potentially useful tool to augment functional movement; however, with data collected at single time point we cannot determine whether functional improvement with SRS could be sustained with longitudinal use. Future studies with participants using SRS routinely in daily life will help determine whether wearable SRS devices may be efficacious assistive devices. In addition, because sensory integration is a central prerequisite for effective motor development, SRS may have value as a therapeutic tool for motor learning and enable participants with sensory-motor impairments to develop more efficient, fast, variable, and complex movements. It is important to note that our study and prior literature on SRS therapy do not find any harm to participants.

Medical treatments for spasticity, including muscle relaxants and botulinum toxin, can have adverse effects such as sedation and muscle atrophy, and can have high cost.[59-61] SRS therapy, by comparison, could present a very cost-effective adjunct to supporting motor function. Future studies could address the effects of SRS when coupled with intensive rehabilitation training like CIMT, or when used in functional, purposeful play opportunities to enrich motor learning. Future studies could also explore the effect of SRS stimulation to support neuroplasticity and motor development in early infancy.

Study limitations

Participants were screened for major cognitive and language impairment prior to participation; however, not all participants had the behavioral regulation to complete all the proposed study procedures. Some participants had difficulty understanding specific tasks. For example, during the SHUEE, many participants had difficulty understanding the task of touching the contralateral ear or extending their hand and supinating to receive "five." Failure to understand the task may have influenced their actual performance and the score given by the video reviewer.

Study participants completed motor tests in either two or three conditions in a single session, with each testing round lasting, at times, over 15 minutes. Some participants may have unintentional benefits of massed practice in a single session. We tried to limit the effect of practice on the outcome measure by varying whether treatment or sham was presented first, but there was an uneven distribution, with nine participants measured first in the sham condition and six participants first assessed in the treatment condition. In future studies, a blocked, randomized design can be used to ensure a more equal distribution between treatment conditions.

Placement of SRS was chosen based on where the bracelets and arm bands were designed to fit, not necessarily because these locations are known to be optimal. We chose the 80% to 90% threshold for SBT-SRS based on previous reports for this level of noise to maximally enhance neuronal detection of weak signals, yet some participants in this study performed even better with AT-SRS. Further experimentation is needed to determine the optimal placement and intensity of SRS, which may vary from one individual to the next and may also vary whether the desired task involves gross motor function or fine motor function.

CONCLUSION

In this pilot study, children with hemiplegic CP demonstrated improved functioning of their impaired hand in uni-manual and bimanual tasks while receiving SBT-SRS. Evidence suggested that children with hemiplegic CP may receive greater benefit from AT-SRS. Future research should examine the optimal intensity, duration, and long-term effect of SRS for impaired hand function.

DISCLOSURE

There are no conflicts of interest.

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REFERENCES

1. Krigger KW. Cerebral palsy: an overview. *AFP*. 2006;73(1):91-100.
2. Cooper J, Majnemer A, Rosenblatt B, Birnbaum R. The determination of sensory deficits in children with hemiplegic cerebral palsy. *J Child Neurol*. 1995;10(4):300-309. doi:10.1177/088307389501000412
3. Honeycutt A, Dunlap L, Chen H, Homsi G, Grosse, S. D, Schendel, D. E, et al. *Economic Costs Associated with Mental Retardation*, *Cerebral Palsy*, *Hearing Loss*, *and Vision Impairment United States*, 2003. Vol 53. U.S. Center for Disease Control; 2004:57–59. Accessed December 27, 2020. http://search.proquest.com/docview/203707639/abstract/299D97F027984C96PQ/1
4. Proske U, Gandevia SC. The proprioceptive senses: their roles in signaling body shape, body position and movement, and muscle force. *Physiol Rev*. 2012;92(4):1651-1697. doi:10.1152/physrev.00048.2011
5. Zoia S, Blason L, D'Ottavio G, Biancotto M, Bulgheroni M, Castiello U. The development of upper limb movements: from fetal to post-Natal life. *PLOS One*. 2013;8(12):e80876. doi:10.1371/journal.pone.0080876
6. Corbetta D, Snapp-Childs W. Seeing and touching: the role of sensory-motor experience on the development of infant reaching. *Infant Behav Dev*. 2009;32(1):44-58. doi:10.1016/j.infbeh.2008.10.004
7. Bleyenheuft Y, Gordon AM. Precision grip control, sensory impairments and their interactions in children with hemiplegic cerebral palsy: a systematic review. *Res Dev Disabil*. 2013;34(9):3014-3028. doi:10.1016/j.ridd.2013.05.047
8. Wingert JR, Burton H, Sinclair RJ, Brunstrom JE, Damiano DL. Tactile sensory abilities in cerebral palsy: deficits in roughness and object discrimination. *Dev Med Child Neurol*. 2008;50(11):832-838.
9. Van Heest AE, House J, Putnam M. Sensibility deficiencies in the hands of children with spastic hemiplegia. *J Hand Surg Am*. 1993;18(2):278-281. doi:10.1016/0363-5023(93)90361-6
10. Matusz PJ, Key AP, Gogliotti S, et al. Somatosensory plasticity in pediatric cerebral palsy following constraint-induced movement therapy. *Neural Plast*. 2018;2018:1-14. doi:10.1155/2018/1891978
11. Zarkou A, Lee SCK, Prosser LA, Jeka JJ. Foot and ankle somatosensory deficits affect balance and motor function in children with cerebral palsy. *Front Hum Neurosci*. 2020;14:45-56. https://doi.org.proxy.library.vcu.edu/10.3389/fnhum.2020.00045
12. Auld ML, Boyd R, Moseley GL, Ware R, Johnston LM. Tactile function in children with unilateral cerebral palsy compared to typically developing children. *Disabil Rehabil*. 2012;34(17):1488-1494. doi:10.3109/09638288.2011.650314
13. Goble DJ, Hurvitz EA, Brown SH. Deficits in the ability to use proprioceptive feedback in children with hemiplegic cerebral

palsy. *Int J Rehabil Res*. 2009;32(3):267-269. doi:10.1097/MRR.0b013e32832a62d5
14. Goble DJ, Aaron MB, Warschausky S, Kaufman JN, Hurvitz EA. The influence of spatial working memory on ipsilateral remembered proprioceptive matching in adults with cerebral palsy. *Exp Brain Res*. 2012;223(2):259-269. doi:10.1007/s00221-012-3256-8
15. Riquelme I, Montoya P. Developmental changes in somatosensory processing in cerebral palsy and healthy individuals. *Clin Neurophysiol*. 2010;121(8):1314-1320. doi:10.1016/j.clinph.2010.03.010
16. Nevalainen P, Pihko E, Mäenpää H, Valanne L, Nummenmaa L, Lauronen L. Bilateral alterations in somatosensory cortical processing in hemiplegic cerebral palsy. *Dev Med Child Neurol*. 2012;54(4):361-367. doi:10.1111/j.1469-8749.2011.04165.x
17. Auld ML, Boyd RN, Moseley GL, Ware RS, Johnston LM. Impact of tactile dysfunction on upper-limb motor performance in children with unilateral cerebral palsy. *Arch Phys Med Rehabil*. 2012;93(4):696-702. doi:10.1016/j.apmr.2011.10.025
18. Auld ML, Johnston LM. Perspectives on tactile intervention for children with cerebral palsy: a framework to guide clinical reasoning and future research. *Disabil Rehabil*. 2018;40(15):1849-1854. doi:10.1080/09638288.2017.1312571
19. MacFarlane C, Hing W, Orr R. Using the Edinburgh visual gait score to compare ankle-foot orthoses, sensorimotor orthoses and barefoot gait pattern in children with cerebral palsy. *Children (Basel)*. 2020;7(6):54-67. doi:10.3390/children7060054
20. Giray E, Keniş-Coşkun Ö, Güngör S, Karadağ-Saygı E. Does stabilizing input pressure orthosis vest, lycra-based compression orthosis, improve trunk posture and prevent hip lateralization in children with cerebral palsy? *Turk J Phys Med Rehabil*. 2017;64(2):100-107. doi:10.5606/tftrd.2018.1332
21. Hylton N, Allen C. The development and use of SPIO Lycra compression bracing in children with neuromotor deficits. *Pediatr Rehabil*. 1997;1(2):109-116. doi:10.3109/17518429709025853
22. Moss F, Ward LM, Sannita WG. Stochastic resonance and sensory information processing: a tutorial and review of application. *Clin Neurophysiol*. 2004;115(2):267-281. doi:10.1016/j.clinph.2003.09.014
23. Douglass JK, Wilkens L, Pantazelou E, Moss F. Noise enhancement of information transfer in crayfish mechanoreceptors by stochastic resonance. *Nature*. 1993;365(6444):337-340. doi:10.1038/365337a0
24. Chiou-Tan FY, Magee KN, Robinson LR, et al. Enhancement of subthreshold sensory nerve action potentials during muscle tension mediated noise. *Int J Bifurcat Chaos*. 1996;06(07):1389-1396. doi:10.1142/S0218127496000813
25. Ward LM, Neiman A, Moss F. Stochastic resonance in psychophysics and in animal behavior. *Biol Cybern*. 2002;87(2):91-101. https://doi.org.proxy.library.vcu.edu/10.1007/s00422-002-0328-z
26. Collins JJ, Imhoff TT, Grigg P. Noise-enhanced tactile sensation. *Nature*. 1996;383(6603):770-770. doi:10.1038/383770a0
27. Simonotto E, Spano F, Riani M, et al. fMRI studies of visual cortical activity during noise stimulation. *Neurocomputing*. 1999;26-27:511-516. doi:10.1016/S0925-2312(99)00042-9
28. Enders LR, Hur P, Johnson MJ, Seo NJ. Remote vibrotactile noise improves light touch sensation in stroke survivors' fingertips via stochastic resonance. *J Neuroeng Rehabil*. 2013;10(1):105. doi:10.1186/1743-0003-10-105
29. Breen PP, ÓLaighin G, McIntosh C, Dinneen SF, Quinlan LR, Serrador JM. A new paradigm of electrical stimulation to enhance sensory neural function. *Med Eng Phys*. 2014;36(8):1088-1091. doi:10.1016/j.medengphy.2014.04.010
30. Dhruv NT, Niemi JB, Harry JD, Lipsitz LA, Collins JJ. Enhancing tactile sensation in older adults with electrical noise stimulation. *Neuroreport*. 2002;13(5):597-600. doi:10.1097/00001756-200204160-00012
31. Khaodhiar L, Niemi JB, Earnest R, Lima C, Harry JD, Veves A. Enhancing sensation in diabetic neuropathic foot with mechanical noise. *Diabetes Care*. 2003;26(12):3280-3283. doi:10.2337/diacare.26.12.3280
32. Cloutier R, Horr S, Niemi JB, et al. Prolonged mechanical noise restores tactile sense in diabetic neuropathic patients. *Int J Low Extrem Wounds*. 2009;8(1):6-10. doi:10.1177/1534734608330522
33. Kurita Y, Shinohara M, Ueda J. Wearable sensorimotor enhancer for fingertip based on stochastic resonance effect. *IEEE Trans Hum-Mach Syst*. 2013;43(3):333-337. doi:10.1109/TSMC.2013.2242886
34. Costa M, Priplata AA, Lipsitz LA, et al. Noise and poise: enhancement of postural complexity in the elderly with a stochastic-resonance–based therapy. *Europhys Lett*. 2007;77(6):68008. doi:10.1209/0295-5075/77/68008
35. Lipsitz LA, Lough M, Niemi J, Travison T, Howlett H, Manor B. A shoe insole delivering subsensory vibratory noise improves balance and gait in healthy elderly people. *Arch Phys Med Rehabil*. 2015;96(3):432-439. doi:10.1016/j.apmr.2014.10.004
36. Miranda DL, Hsu WH, Gravelle DC, et al. Sensory enhancing insoles improve athletic performance during a hexagonal agility task. *J Biomech*. 2016;49(7):1058-1063. doi:10.1016/j.jbiomech.2016.02.022
37. Zarkou A, Lee SCK, Prosser LA, Hwang S, Jeka J. Stochastic resonance stimulation improves balance in children with cerebral palsy: a case control study. *J Neuroeng Rehabil*. 2018;15:115. https://doi.org.proxy.library.vcu.edu/10.1186/s12984-018-0467-7
38. Stocks NG. Suprathreshold stochastic resonance in multilevel threshold systems. *Phys Rev Lett*. 2000;84(11):2310-2313. doi:10.1103/PhysRevLett.84.2310
39. Stocks NG. Information transmission in parallel threshold arrays: Suprathreshold stochastic resonance. *Phys Rev E.* 2001;63(4):041114. doi:10.1103/PhysRevE.63.041114
40. Eliasson AC, Krumlinde-Sundholm L, Rösblad B, et al. The manual ability classification system (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. *Dev Med Child Neurol*. 2006;48(7):549-554. doi:10.1017/S0012162206001162
41. Mutlu A, Livanelioglu A, Gunel MK. Reliability of Ashworth and modified Ashworth scales in children with spastic cerebral palsy. *BMC Musculoskelet Disord*. 2008;9(1):44. doi:10.1186/1471-2474-9-44
42. Sukal-Moulton T, Gaebler-Spira D, Krosschell KJ. The validity and reliability of the test of arm selective control for children with cerebral palsy: a prospective cross-sectional study. *Dev Med Child Neurol*. 2018;60(4):374-381. doi:10.1111/dmcn.13671
43. Lesný I, Stehlík A, Tomásek J, Tománková A, Havlícek I. Sensory disorders in cerebral palsy: two-point discrimination. *Dev Med Child Neurol*. 1993;35(5):402-405. doi:10.1111/j.1469-8749.1993.tb11661.x
44. Raymond B, Steriovski J, Gillyard K, Yang C, Wu SC, Crews RT. Choosing a vibratory test to pair with Semmes Weinstein monofilament testing for evaluating lower extremity sensation in patients with diabetes: a comparison of three vibratory methodologies. *J Diabetes Sci Technol*. 2020;14(1):8-15. doi:10.1177/1932296819849478
45. Araneda R, Ebner-Karestinos D, Paradis J, et al. Reliability and responsiveness of the Jebsen-Taylor test of hand function and the box and block test for children with cerebral palsy. *Dev Med Child Neurol*. 2019;61(10):1182-1188. doi:10.1111/dmcn.14184
46. Jongbloed-Pereboom M, MWGN van der S, Steenbergen B. Norm scores of the box and block test for children ages 3–10 years. *Am J Occup Ther*. 2013;67(3):312-318. doi:10.5014/ajot.2013.006643
47. Davids JR, Peace LC, Wagner LV, Gidewall MA, Blackhurst DW, Roberson WM. Validation of the Shriners Hospital for Children Upper Extremity Evaluation (SHUEE) for children

with hemiplegic cerebral palsy. *JBJS*. 2006;88(2):326-333. doi: 10.2106/JBJS.E.00298
48. DeLuca SC, Case-Smith J, Stevenson R, Ramey SL. Constraint-induced movement therapy (CIMT) for young children with cerebral palsy: effects of therapeutic dosage. *J Pediatr Rehabil Med*. 2012;5(2):133-142. doi:10.3233/PRM-2012-0206
49. Collins JJ, Imhoff TT, Grigg P. Noise-mediated enhancements and decrements in human tactile sensation. *Phys Rev E*. 1997; 56(1):923-926. doi:10.1103/PhysRevE.56.923
50. Hijmans JM, Geertzen JHB, Schokker B, Postema K. Development of vibrating insoles. *Int J Rehabil Res*. 2007;30(4):343-345. doi:10.1097/MRR.0b013e3282f14469
51. Priplata AA, Patritti BL, Niemi JB, et al. Noise-enhanced balance control in patients with diabetes and patients with stroke. *Ann Neurol*. 2006;59(1):4-12. doi:10.1002/ana.20670
52. Priplata A, Niemi J, Salen M, Harry J, Lipsitz LA, Collins JJ. Noise-enhanced human balance control. *Phys Rev Lett*. 2002; 89(23):238101. doi:10.1103/PhysRevLett.89.238101
53. Chan YH. Biostatistics 104: correlational analysis. *Singapore Med J*. 2003;44(12):614-619.
54. Charles J, Gordon AM. A critical review of constraint-induced movement therapy and forced use in children with hemiplegia. *Neural Plast*. 2005;12((2–3)):245-261; discussion 263–272. doi: 10.1155/NP.2005.245
55. Chen HM, Chen CC, Hsueh IP, Huang SL, Hsieh CL. Test-retest reproducibility and smallest real difference of 5 hand function tests in patients with stroke. *Neurorehabil Neural Repair*. 2009; 23(5):435-440. doi:10.1177/1545968308331146
56. Yoon JA, Koo BI, Shin MJ, Shin YB, Ko HY, Shin YI. Effect of constraint-induced movement therapy and Mirror therapy for patients with subacute stroke. *Ann Rehabil Med*. 2014;38(4): 458-466. doi:10.5535/arm.2014.38.4.458
57. Siebers A, Öberg U, Skargren E. The effect of modified constraint-induced movement therapy on spasticity and motor function of the affected arm in patients with chronic stroke. *Physiother Can*. 2010;62(4):388-396. doi:10.3138/physio.62.4.388
58. Stein J, Hughes R, D'Andrea S, et al. Stochastic resonance stimulation for upper limb rehabilitation Poststroke. *Am J Phys Med Rehabil*. 2010;89(9):697-705. doi:10.1097/PHM.0b013e3181ec9aa8
59. Ertzgaard P, Campo C, Calabrese A. Efficacy and safety of oral baclofen in the management of spasticity: a rationale for intrathecal baclofen. *J Rehabil Med*. 2017;49(3):193-203. doi: 10.2340/16501977-2211
60. Multani I, Manji J, Hastings-Ison T, Khot A, Graham K. Botulinum toxin in the Management of Childrenwith Cerebral Palsy. *Pediatr Drugs*. 2019;21(4):261-281. doi:10.1007/s40272-019-00344-8
61. Van Campenhout A, Verhaegen A, Pans S, Molenaers G. Botulinum toxin type a injections in the psoas muscle of children with cerebral palsy: muscle atrophy after motor end plate-targeted injections. *Res Dev Disabil*. 2013;34(3):1052-1058. doi: 10.1016/j.ridd.2012.11.016

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