Cerebral Palsy ALLIANCE

NEWS
Cerebral Palsy Research

Monday 17 September 2018

Cerebral Palsy Alliance is delighted to bring you this free weekly bulletin of the latest published research into cerebral palsy. Our organisation is committed to supporting cerebral palsy research worldwide - through information, education, collaboration and funding. Find out more at research.cerebralpalsy.org.au

Professor Nadia Badawi AM
Macquarie Group Foundation Chair of Cerebral Palsy

Subscribe to CP Research News

Interventions and Management

1. Patterns of upper limb muscle activation in children with unilateral spastic cerebral palsy: Variability and detection of deviations.
Sarcher A, Brochard S, Hug F, Letellier G, Raison M, Perrouin-Verbe B, Sangeux M, Gross R.

Clin Biomech (Bristol, Avon). 2018 Sep 5;59:85-93. doi: 10.1016/j.clinbiomech.2018.09.005. [Epub ahead of print]

BACKGROUND: The aim of this study was two-fold: (1) to quantify the variability of upper limb electromyographic patterns during elbow movements in typically developing children and children with unilateral spastic cerebral palsy, and to compare different amplitude normalization methods; (2) to develop a method using this variability to detect (a) deviations in the patterns of a child with unilateral spastic cerebral palsy from the average patterns of typically developing children, and (b) changes after treatment to reduce muscle activation. METHODS: Twelve typically developing children ([6.7-15.9yo]; mean 11.0 SD 3.0yo) and six children with unilateral spastic cerebral palsy ([7.9-17.4yo]; mean 12.4 SD 4.0yo) attended two sessions during which they performed elbow extension-flexion and pronation-supination movements. Surface electromyography of the biceps, triceps, brachioradialis, pronator teres, pronator quadratus, and brachialis muscles was recorded. The Likelihood method was used to estimate the inter-trial, inter-session, and inter-subject variability of the electromyography patterns for each time point in the movement cycle. Deviations in muscle patterns from the patterns of typically developing children and changes following treatment were evaluated in a case study of a child with cerebral palsy. FINDINGS: Normalization of electromyographic amplitude by the mean peak yielded the lowest variability. The variability data were then used in the case study. This method detected higher levels of activation in specific muscles compared with typically developing children, and a reduction in muscle activation after botulinum toxin A injections. INTERPRETATION: Upper limb surface electromyography pattern analysis can be used for clinical applications in children with cerebral palsy.

PMID: 30216783

2. Upper-limb contracture development in children with cerebral palsy: a population-based study.
Hedberg-Graff J, Granström F, Arner M, Krumlinde-Sundholm L.

Dev Med Child Neurol. 2018 Sep 10. doi: 10.1111/dmcn.14006. [Epub ahead of print]

AIM: The aim of this study was to investigate the longitudinal development of passive range of motion (ROM) in the upper limbs in a population-based sample of children with cerebral palsy (CP), and to investigate which children are more likely to develop contractures related to functional level, CP subtype, and age. METHOD: Registry data of annual passive ROM measurements of the upper limbs from 771 children with CP (417 males, 354 females; mean age 11y 8mo, [SD 5mo] range 1-18y) were analysed. Mixed models were used to investigate at what age decreased passive ROM occurs. Odds ratios were calculated to compare risks and logistic regression analysis was used to predict contracture development. RESULTS: Thirty-four per cent of the children had developed contractures. Among these children, decreased passive ROM was significant at a

mean age of 4 years for wrist extension and 7 years for shoulder flexion, elbow extension, and supination. Children at Manual Ability Classification System (MACS) level V had a 17-times greater risk of contractures than children at MACS level I. INTERPRETATION: One-third of the children in the total population developed upper-limb contractures while passive ROM decreased with age. MACS level was the strongest predictor of contracture development. WHAT THIS PAPER ADDS: In a population-based sample of 771 children with cerebral palsy, 34% developed an upper-limb contracture. Contracture development started at preschool age. The first affected movements were wrist extension and supination. Passive range of motion decreased with age. High Manual Ability Classification System level was the most important predictor of contractures.

PMID: 30203516

3. Development of a Pediatric Goal-Centered Upper Limb Spasticity Home Exercise Therapy Program for Use in a Phase-III Trial of Abobotulinumtoxina (Dysport®).
Shierk A, Jiménez-Moreno AC, Roberts H, Ackerman-Laufer S, Backer G, Bard-Pondarre R, Cekmece C, Pyrzanowska W, Vilain C, Delgado MR.

Phys Occup Ther Pediatr. 2018 Sep 11:1-12. doi: 10.1080/01942638.2018.1486346. [Epub ahead of print]

AIMS: To create a standardized home exercise therapy program that could be implemented by international sites to provide a consistent level of therapeutic intervention for pediatric patients participating in an ongoing Phase-III, randomized, controlled trial of repeat abobotulinumtoxinA injections for pediatric upper limb spasticity (NCT02106351). METHODS: Physical therapists, occupational therapists, and medical doctors worked collaboratively to design an exercise therapy program to be implemented in the home setting. In this article, we describe the development process and the finalized program that is currently being used in the Phase-III trial. RESULTS: The final program is presented as a "toolbox" for therapists, and includes a standardized step-wise process for choosing the most appropriate exercises and functional activities to achieve the agreed treatment goals of each abobotulinumtoxinA injection. The core toolbox includes: a clear protocol for clinicians, information sheets, signature of commitment forms, exercise score charts, and the library of exercises and functional activities that therapists choose from to aid the patient in achieving their treatment goals. CONCLUSIONS: Implementation of this home therapy program provides a standardized background of good practice against which to test the efficacy of abobotulinumtoxinA. Preliminary data show that the program is readily accepted by patients and their families.

PMID: 30204515

4. Current Therapeutic Management of Perinatal Stroke with a Focus on the Upper Limb: A Cross-Sectional Survey of UK Physiotherapists and Occupational Therapists.
Marcroft C, Tsutsumi A, Pearse J, Dulson P, Embleton ND, Basu AP.

Phys Occup Ther Pediatr. 2018 Sep 13:1-17. doi: 10.1080/01942638.2018.1503212. [Epub ahead of print]

AIM: To determine current UK pediatric physiotherapist (PT) and occupational therapist (OT) management of perinatal stroke. DESIGN: Web-based cross-sectional survey. METHODS: Participants were members of the Association of Paediatric Chartered Physiotherapists and Occupational Therapists specialist section: children young people and families working with infants. Items covered prioritization of referrals, assessments, therapy approaches aimed at the upper limb, and parental support. RESULTS: 179 therapists responded. 87.2% of PTs and 63.0% of OTs managed infants with perinatal stroke. Infants with clinical signs of motor dysfunction at referral were prioritized for early initial assessment. The most frequently used assessments were the Alberta Infant Motor Scale (AIMS) and Bayley Scales of Infant Development (BSID). Of PTs and OTs, 41.9 and 40.0% used no standardized assessments. Frequently used therapy interventions were Bobath/Neurodevelopmental Therapy (NDT), positioning aids and passive movements. 88.1% of therapists would choose a bilateral rather than unilateral (affected side) therapy approach for infants with perinatal stroke aged up to 6 months. Of PTs and OTs, 56.9 and 57.1% provided psychological support to families. CONCLUSIONS: Assessment and provision of therapy services following perinatal stroke is variable. Increased use of standardized assessments and centralized data collection regarding service provision for high-risk infants is recommended.

PMID: 30211625

5. Effects of a Gaming Platform on Balance Training for Children With Cerebral Palsy.
Hsieh HC.

Pediatr Phys Ther. 2018 Sep 6. doi: 10.1097/PEP.0000000000000521. [Epub ahead of print]

PURPOSE: A platform requiring multidimensional trunk movement facilitated postural balance in children with cerebral palsy. METHODS: The intervention group (n = 20) received 12 weeks of playing personal computer (PC) games using the platform, and the control group (n = 20) played the same games using a computer mouse. Outcomes were center-of-pressure sway, the Berg Balance Scale (BBS), Fullerton Advanced Balance Scale (FAB), and Timed Up and Go (TUG) test scores. RESULTS: There were significant interactions between groups and time. There was a significant between-group difference in center-of-pressure sway excursion, BBS test, and TUG test over time. Participants in the intervention group had better balance performance compared with the control group. CONCLUSION: Balance training using a PC gaming platform may improve exercise compliance and enhance recovery of balance in children with cerebral palsy.

PMID: 30199515

6. Selective motor control and gross motor function in bilateral spastic cerebral palsy.
Noble JJ, Gough M, Shortland AP.

Dev Med Child Neurol. 2018 Sep 10. doi: 10.1111/dmcn.14024. [Epub ahead of print]

AIM: To investigate the relationship between selective motor control (SMC), muscle volume, and spasticity with gross motor function in adolescents and young adults with bilateral spastic cerebral palsy (CP). METHOD: Eleven male participants with CP (mean age 15y 7mo, standard deviation 3y 6mo, range 12y 1mo-23y 1mo) in Gross Motor Function Classification System (GMFCS) levels I to IV took part in this cross-sectional study. Magnetic resonance imaging (MRI) of both lower limbs of all participants were acquired, from which 18 muscles were manually segmented and muscle volume calculated by a single assessor. Muscle volumes were normalized to body mass and averaged between limbs for each individual. SMC was assessed using Selective Control Assessment of the Lower Extremity (SCALE). Spasticity was assessed using the Modified Ashworth Scale (MAS), and gross motor functional ability was assessed using the Gross Motor Function Measure (GMFM-66). RESULTS: GMFM-66 was strongly positively correlated to SCALE ($r=0.901$, $p\leq0.001$) and lower limb muscle volume normalized to body mass ($r=0.750$, $p=0.008$). MAS was significantly correlated with GMFM-66 ($r=-0.691$, $p=0.018$). INTERPRETATION: SMC is a major factor influencing gross motor function in individuals with CP. Lower limb muscle volume and spasticity also influence gross motor function. WHAT THIS PAPER ADDS: Selective motor control is a major factor of gross motor function in adolescents and young adults with bilateral cerebral palsy (CP). Gross motor function is related to muscle size and level of spasticity in adolescents and young adults with bilateral CP.

PMID: 30203469

7. Skeletal Muscle Adaptations and Passive Muscle Stiffness in Cerebral Palsy: A Literature Review and Conceptual Model.
Tisha AL, Armstrong AA, Wagoner Johnson A, Lopez-Ortiz C.

J Appl Biomech. 2018 Sep 12:1-37. doi: 10.1123/jab.2018-0049. [Epub ahead of print]

This literature review focuses on the primary morphological and structural characteristics, and mechanical properties identified in muscles affected by spastic cerebral palsy (CP). CP is a non-progressive neurological disorder caused by brain damage and is commonly diagnosed at birth. Although the brain damage is not progressive, subsequent neuro-physiological developmental adaptations may initiate changes in muscle structure, function, and composition, causing abnormal muscle activity and coordination. The symptoms of CP vary among patients. However, muscle spasticity is commonly present and is one of the most debilitating effects of CP. Here, we present the current knowledge regarding the mechanical properties of skeletal tissue affected by spastic CP. An increase in sarcomere length, collagen content, and fascicle diameter, and a reduction in the number of satellite cells within spastic CP muscle were consistent findings in the literature. Studies differed, however, in changes in fascicle lengths and fiber diameters. We also present a conceptual mechanical model of fascicle force transmission that incorporates mechanisms that impact both serial and lateral force production, highlighting the connections between the macro and micro structures of muscle to assist in deducing specific mechanisms for property changes and reduced force production.

PMID: 30207207

8. Trabecular bone score in adults with cerebral palsy.
Trinh A, Wong P, Fahey MC, Ebeling PR, Fuller PJ, Milat F.

Bone. 2018 Sep 5;117:1-5. doi: 10.1016/j.bone.2018.09.001. [Epub ahead of print]

CONTEXT: Bone fragility in cerebral palsy (CP) is secondary to a complex interplay of functional, hormonal, and nutritional factors that affect bone remodelling. A greater understanding of bone microarchitectural changes seen in CP should assist therapeutic decision making. OBJECTIVE: To examine the relationship between trabecular bone score (TBS), BMD and fractures in adults with CP; the influence of clinical factors and body composition on bone microarchitecture were explored. DESIGN: Retrospective cross-sectional study. SETTING AND PARTICIPANTS: 43 adults (25 male) with CP of median age 25 years (interquartile range 21.4-33.9) who had evaluable dual-energy X-ray absorptiometry imaging of the lumbar spine from a single tertiary hospital between 2005-March 2018. RESULTS: 24/43 (55.8%) of patients had TBS values indicating intermediate or high risk of fracture (<1.31). TBS correlated with areal BMD at the lumbar spine, femoral neck and total body. TBS was significantly associated with arm and leg lean mass, with adjustment for age, gender and height (adjusted $R2 = 0.18$, $p = 0.042$ for arm lean mass; adjusted $R2 = 0.19$, $p = 0.036$ for leg lean mass). There was no difference in TBS when patients were grouped by fracture status, anticonvulsant use, gonadal status or use of PEG feeding. TBS was lower in non-ambulatory patients compared with ambulatory patients (1.28 vs 1.37, $p = 0.019$). CONCLUSIONS: Abnormal bone microarchitecture, as measured by TBS, was seen in >50% of young adults with CP. TBS correlated with both areal BMD and appendicular lean mass. Maintaining muscle function is likely to be important for bone health in young adults with CP and needs to be confirmed in further studies.

PMID: 30193871

9. Functional strength measurement in cerebral palsy: feasibility, test-retest reliability, and construct validity.
Aertssen W, Smulders E, Smits-Engelsman B, Rameckers E.

Dev Neurorehabil. 2018 Sep 12:1-9. doi: 10.1080/17518423.2018.1518963. [Epub ahead of print]

PURPOSE: No instrument exists that measures functional strength in both lower and upper extremities in children with cerebral palsy (CP). Therefore, the functional strength measurement (FSM) was tested for feasibility, test-retest reliability and validity in CP. METHODS: Thirty-seven children with CP (aged 4-10 years, Gross Motor Function Classification System I and II) participated. The most common compensations for CP were described; new item descriptions were standardized, and one item was removed. Test-retest reliability was examined. To measure convergent validity, correlations between the FSM-CP and isometric muscle strength measured with the handheld dynamometer (HHD) were determined. RESULTS: Test-retest reliability was considered high for all items (intra-class correlation coefficient 0.79-0.95). Significant correlations between the HHD and FSM-CP ranged from $r = 0.36$ to 0.75. CONCLUSION: The FSM-CP is feasible, reliable, and valid to use in children with CP. The FSM-CP can be considered as a helpful tool in clinical practice of physical examination of children with CP.

PMID: 30207812

10. Transcranial Direct-Current Stimulation on Motor Function in Pediatric Cerebral Palsy: A Systematic Review.
Hamilton A, Wakely L, Marquez J.

Pediatr Phys Ther. 2018 Sep 6. doi: 10.1097/PEP.0000000000000535. [Epub ahead of print]

PURPOSE: To determine effects of transcranial direct-current stimulation (tDCS) on motor function for children with cerebral palsy. METHODS: Six electronic databases were searched using terms related to tDCS, combined with functional deficits/ associated clinical measures. Results were filtered, including randomized controlled trials in English and children with cerebral palsy. Data were extracted using standardized procedures, and the PEDro scale was used to assess quality and meta-analyses conducted. RESULTS: From 135 articles, 9 studies with moderate quality met inclusion criteria. Six were included in 7 separate meta-analyses supporting a benefit of tDCS for static balance, only at follow-up. Benefits of tDCS on dynamic balance, step length, and mobility were not established. CONCLUSIONS: The findings from meta-analyses suggest that tDCS may provide improvements in static balance at follow-up in children with cerebral palsy and positive effects on gait velocity; however, there was heterogeneity. Further research is needed before this therapy can be endorsed.

PMID: 30199513

11. The efficacy of kinesiology taping for improving gross motor function in children with cerebral palsy: A systematic review.
Unger M, Carstens JP, Fernandes N, Pretorius R, Pronk S, Robinson AC, Scheepers K.

S Afr J Physiother. 2018 Aug 29;74(1):459. doi: 10.4102/sajp.v74i1.459. eCollection 2018.

BACKGROUND: Kinesiology taping is an increasingly popular technique used as an adjunct to physiotherapy intervention for children with cerebral palsy (CP), but as yet we do not have a review of the available evidence as to its efficacy. OBJECTIVES: To critically appraise and establish best available evidence for the efficacy of truncal application of kinesiology taping combined with physiotherapy, versus physiotherapy alone, on gross motor function (GMF) in children with CP. METHOD: Seven databases were searched using the terms CP, kinesio taping and/or kinesiology tape and/or taping, physiotherapy and/or physical therapy and GMF. Only randomised controlled trials (RCTs) were included and appraised using the PEDro scale. Revman© Review Manager was used to combine effects for GMF in sitting, standing and activities of daily living. RESULTS: Five level IIB RCTs that scored 3-6/8 on the PEDro scale were included. Meta-analysis showed that taping was effective for improving GMF in sitting and standing as measured by the Gross Motor Function Measure (B) ($p < 0.001$) and (D) ($p < 0.001$), respectively. CONCLUSION: There is moderate evidence to support kinesiology taping applied to the trunk as an effective intervention when used as an adjunct to physiotherapy to improve GMF in children with CP, especially those with GMF Classification Scale levels I and II, and particularly for improving sitting control. CLINICAL IMPLICATIONS: Kinesiology taping is a useful adjunct to physiotherapy intervention in higher functioning children with CP. Current evidence however is weak and further research into methods of truncal application is recommended.

PMID: 30214950

12. Feasibility of an intensive outpatient Perception-Action Approach intervention for children with cerebral palsy: a pilot study.
Pottinger HL, Rahlin M, Voigt J, Walsh ME, Fregosi CM, Duncan BR.

Physiother Theory Pract. 2018 Sep 10:1-16. doi: 10.1080/09593985.2018.1517847. [Epub ahead of print]

PURPOSE: The purpose of this pilot study was (1) to evaluate feasibility of attendance and parent satisfaction with an intensive outpatient physical and occupational therapy program for young children with spastic cerebral palsy (CP) and (2) to examine changes in motor function. METHODS: Sixteen children with CP, age range 18-36 months (mean 24.3 ± 6.3 months), received physical and occupational therapy sessions (30 minutes each) 5 days per week for 12 weeks. Attendance rates and parent satisfaction were assessed. Change in motor function using a one-group pre-post design was evaluated using the Gross Motor Function Measure-66 (GMFM-66), Quality of Upper Extremity Skills Test, and Pediatric Evaluation of Disability Inventory. GMFM-66 outcomes were also compared with expected outcomes using previously published normative developmental trajectories of children receiving standard therapies. RESULTS: An average of 82% of scheduled outpatient physical and occupational therapies for 16 children were completed and the 11 parents who completed the Hills and Kitchen's Physiotherapy Outpatient Satisfaction Questionnaire were satisfied with the therapies and with their child's progress. Participants showed notable, statistically significant improvement across all activity-related measures. CONCLUSION: An intensive protocol of outpatient therapies utilizing Perception-Action Approach was feasible for most families of young children with spastic CP to attend at the outpatient clinic location. As this was not an experimental study, no reliable conclusions related to efficacy can be made, but the promising results suggest that further research into the effectiveness of intensive protocols is worthwhile.

PMID: 30198809

13. Long-term sustained effect of gait training using a hybrid assistive limb on gait stability via prevention of knee collapse in a patient with cerebral palsy: a case report.
Endo Y, Mutsuzaki H, Mizukami M, Yoshikawa K, Kobayashi Y, Yozu A, Mataki Y, Nakagawa S, Iwasaki N, Yamazaki M.

J Phys Ther Sci. 2018 Sep;30(9):1206-1210. doi: 10.1589/jpts.30.1206. Epub 2018 Sep 4.

[Purpose] The hybrid assistive limb was developed to improve the kinematics and muscle activity in patients with neurological and orthopedic conditions. The purpose of the present study was to examine the long-term sustained effect of gait training using a hybrid assistive limb on gait stability, kinematics, and muscle activity by preventing knee collapse in a patient with cerebral palsy. [Participant and Methods] A 17 year-old male with cerebral palsy performed gait training with a hybrid assistive

limb 12 times in 4 weeks. After completion of 12 sessions of hybrid assistive limb training, monthly follow-up was conducted for 8 months. The improvement was assessed on the basis of joint angle and muscle activity during gait. [Results] The degree of knee collapse observed at baseline was improved at 8-month follow-up. Regarding muscle activity, electromyography revealed increased activation of the vastus lateralis at 8-month follow-up. Moreover, the hip and knee angles were expanded during gait. In particular, the knee extension angle at heel contact was increased at 8 months after follow-up. [Conclusion] Gait training with a hybrid assistive limb provided improvement of gait stability such as kinematics and muscle activity in a patient with cerebral palsy. The improved gait stability through prevention of knee collapse achieved with hybrid assistive limb training sustained for 8 months.

PMID: 30214126

14. Correlation between the Gait Deviation Index and skeletal muscle mass in children with spastic cerebral palsy.
Matsunaga N, Ito T, Noritake K, Sugiura H, Kamiya Y, Ito Y, Mizusawa J, Sugiura H.

J Phys Ther Sci. 2018 Sep;30(9):1176-1179. doi: 10.1589/jpts.30.1176. Epub 2018 Sep 4.

[Purpose] This study aimed to identify a simple and useful muscle parameter for use with the Gait Deviation Index in assessment of ambulatory children with unilateral and bilateral spastic cerebral palsy. [Participants and Methods] Twenty-eight patients (aged 6 to 18 years; 16 females and 12 males) participated in this cross-sectional study. Outcome measurements included the Gait Deviation Index, grip strength, 5-repetition chair stand test, upper limb skeletal muscle mass index, and lower limb skeletal muscle mass index. [Results] By multiple regression analysis, significant independent correlations were observed between the Gait Deviation Index and 5-repetition chair stand test and the Gait Deviation Index and lower limb skeletal muscle mass index, but not between the Gait Deviation Index and grip strength or upper limb skeletal muscle mass index. [Conclusion] The Gait Deviation Index was correlated with lower limb muscle mass in children with spastic cerebral palsy. Determination of lower limb muscle mass may be useful gait evaluation.

PMID: 30214121

15. How do children with bilateral spastic cerebral palsy manage walking on inclines?
Yılmaz Topçuoğlu MS, Krautwurst BK, Klotz M, Dreher T, Wolf SI.

Gait Posture. 2018 Aug 28;66:172-180. doi: 10.1016/j.gaitpost.2018.08.032. [Epub ahead of print]

BACKGROUND: Walking on inclined surfaces is an everyday task, which challenges stability and propulsion even in healthy adults. Children with cerebral palsy adapt similarly to inclines like healthy children do. However, how stability and propulsion in these subjects are influenced by different inclines remained unaddressed as of yet. RESEARCH QUESTION: The aim was to examine the feeling of safety, stability and propulsion of children with cerebral palsy when walking on inclines to gain insight into the challenges they might face on these conditions. METHODS: Eighteen children with bilateral spastic cerebral palsy with gross motor function classification scale level I and II and nineteen healthy children underwent instrumented 3D gait analysis on level ground and on a 5° and a 10° incline. A mixed linear model was used to draw between and within group comparisons. RESULTS: Reduced lateral trunk sway, a relative lengthening of the lower limb at initial contact and a controlled walking speed were employed during downhill gait compared to level walking. Patients showed an increased sagittal ROM of trunk (3-4°) and pelvis (2-3°) and a decreased sagittal knee ROM (13°) compared to the typically developed children. During uphill gait, an insufficient increase of push-off power at the ankle (increase by 0.48 W/kg) was noted in children with CP, which appeared to lead to particularly shorter strides (about 0.1 m) in patients compared to healthy children (increase by 1.32 W/kg). -4°) and pelvis (2-) SIGNIFICANCE: Depending on inclination angle, children with cerebral palsy managed to walk on inclines in a controlled manner. The steeper the incline, the more the gait appeared to be affected: decreased feeling of safety, increased need for stabilising mechanisms for downhill gait and less sufficient uphill propulsion were seen. Helping these patients to attain better control during downhill gait and strengthening uphill gait mechanisms may support their participation in everyday life.

PMID: 30195221

16. The Effectiveness of Botulinum Toxin Type A Injections in the Management of Sialorrhea.
Sürmelioğlu Ö, Dağkıran M, Tuncer Ü, Özdemir S, Tarkan Ö, Çetik F, Kıroğlu M.

Turk Arch Otorhinolaryngol. 2018 Jun;56(2):111-113. doi: 10.5152/tao.2018.2411. Epub 2018 Jun 1.

OBJECTIVE: The aim of this study was to evaluate the effect of Botulinum toxin type A by injecting in the submandibular and parotid glands on the frequency and severity of sialorrhea. METHODS: Pediatric patients who were referred to our department with sialorrhea were evaluated using their parents' frequency and severity scores of sialorrhea with visual analog scales before and after 3 months of botulinum toxin type A injections. Bilateral submandibular and parotid glands were injected with Botulinum toxin type A. RESULTS: Twenty-seven pediatric patients who were referred to our department with a complaint of sialorrhea were included in this study. Seventeen patients were female and 10 were male. Severe sialorrhea with cerebral palsy was present in all the patients. There were no complications after the procedure. CONCLUSION: Botulinum toxin A injected in the major salivary glands in pediatric patients with neurological disorders is a safe and effective method.

PMID: 30197810

17. Do Robotics and Virtual Reality Add Real Progress to Mirror Therapy Rehabilitation? A Scoping Review.
Darbois N, Guillaud A, Pinsault N.

Rehabil Res Pract. 2018 Aug 19;2018:6412318. doi: 10.1155/2018/6412318. eCollection 2018.

BACKGROUND: Mirror therapy has been used in rehabilitation for multiple indications since the 1990s. Current evidence supports some of these indications, particularly for cerebrovascular accidents in adults and cerebral palsy in children. Since 2000s, computerized or robotic mirror therapy has been developed and marketed. OBJECTIVES: To map the extent, nature, and rationale of research activity in robotic or computerized mirror therapy and the type of evidence available for any indication. To investigate the relevance of conducting a systematic review and meta-analysis on these therapies. METHOD: Systematic scoping review. Searches were conducted (up to May 2018) in the Cochrane Library, Google Scholar, IEEE Xplore, Medline, Physiotherapy Evidence Database, and PsycINFO databases. References from identified studies were examined. RESULTS: In sum, 75 articles met the inclusion criteria. Most studies were publicly funded (57% of studies; n = 43), without disclosure of conflict of interest (59% of studies; n = 44). The main outcomes assessed were pain, satisfaction on the device, and body function and activity, mainly for stroke and amputees patients and healthy participants. Most design studies were case reports (67% of studies; n = 50), with only 12 randomized controlled trials with 5 comparing standard mirror therapy versus virtual mirror therapy, 5 comparing second-generation mirror therapy versus conventional rehabilitation, and 2 comparing other interventions. CONCLUSION: Much of the research on second-generation mirror therapy is of very low quality. Evidence-based rationale to conduct such studies is missing. It is not relevant to recommend investment by rehabilitation professionals and institutions in such devices.

PMID: 30210873

18. Implementation of the International Classification of Functioning, Disability, and Health (ICF) Core Sets for Children and Youth with Cerebral Palsy: Global Initiatives Promoting Optimal Functioning.
Schiariti V, Longo E, Shoshmin A, Kozhushko L, Besstrashnova Y, Król M, Neri Correia Campos T, Náryma Confessor Ferreira H, Verissimo C, Shaba D, Mwale M, Amado S.

Int J Environ Res Public Health. 2018 Sep 1;15(9). pii: E1899. doi: 10.3390/ijerph15091899.

Background: The International Classification of Functioning, Disability, and Health (ICF) Core Sets for children and youth with cerebral palsy (CP) offer service providers and stakeholders a specific framework to explore functioning and disability for assessment, treatment, evaluation, and policy purposes in a global context. Objective: Describe global initiatives applying the ICF Core Sets for children and youth with CP, with a focus on contributions to clinical practice and challenges in their implementation. Methods: This is a descriptive cross-sectional study. Ongoing initiatives applying the ICF Core Sets for CP in Russia, Poland, Malawi, and Brazil are included. Results: The main contributions of applying the ICF Core Sets for children and youth with CP include: (1) an objective description of abilities and limitations in everyday activities; (2) a consistent identification of facilitators and barriers influencing functioning; (3) a practical communication tool promoting client-centered care and multidisciplinary teamwork; and, (4) a useful guideline for measurement selection. The main challenges of adopting the ICF Core Sets are related to lack of ICF knowledge requiring intense training and translating results from standardized measures into the ICF qualifiers in a consistent way. Conclusions: Global initiatives include research and clinical applications at the program, service and system levels. The ICF Core Sets for CP are useful tools to guide service provision and build profiles of functioning and disability. Global interprofessional collaboration, capacity training, and informatics (e-records) will maximize their applications and accelerate adoption.

PMID: 30200412

19. Psychometric Properties of Assessments of Cognition in Infants With Cerebral Palsy or Motor Impairment: A Systematic Review.
Morgan C, Honan I, Allsop A, Novak I, Badawi N.

J Pediatr Psychol. 2018 Sep 12. doi: 10.1093/jpepsy/jsy068. [Epub ahead of print]

OBJECTIVE: Approximately 50% of people with cerebral palsy have a cognitive impairment. However, many tools used to assess cognition in infants require almost normal fine motor ability, and thus may not accurately reflect cognitive abilities of infants with cerebral palsy or other motor impairments. This systematic review aimed to evaluate the psychometric properties of cognitive assessment tools for infants aged 0-24 months with motor impairments and to make recommendations about the most appropriate cognitive assessment tools for the purpose of discrimination, prediction, and evaluation. METHOD: A systematic review was conducted. CINAHL, Embase, ERIC, Medline, PsycINFO, and SCOPUS databases were searched to identify studies reporting on 1 or more psychometric properties of a standardized cognitive assessment tool or questionnaire in a sample/subsample of infants with motor impairment. Of the 4,480 articles reviewed, 9 assessment tools were identified in 20 publications, which met our inclusion criteria. Articles were appraised using the COnsensus-based Standards for the selection of health Measurement INstruments to assess study rigor. The GRADE framework was applied to develop recommendations for clinical practice. RESULTS: The Mayes Motor-Free Compilation, Fagan Test of Infant Intelligence, and Bayley-III Low Motor/Vision have predictive and/or discriminative utility in this population. The Mullen Scales of Early Learning was the only tool with psychometric research available examining responsivity to change. CONCLUSIONS: Assessment tools with low-motor/motor-free accommodations have greater accuracy in estimating cognitive abilities of infants with motor impairment than conventional norm-referenced tests. There, however, remains a significant paucity of research in this area.

PMID: 30215749

20. Pain and sleep issues in Rett syndrome and other neurodevelopmental disorders.
Cappuccio G, Bernardo P, Raiano E, Pinelli M, Alagia M, Esposito M, Della Casa R, Strisciuglio P, Brunetti-Pierri N, Bravaccio C.

Acta Paediatr. 2018 Sep 14. doi: 10.1111/apa.14576. [Epub ahead of print]

Rett syndrome is a severe neurodevelopmental disorder, mostly caused by a MECP2 gene mutation, with some overlaps with autism spectrum disorders and cerebral palsy. Pain perception is potentially abnormal in children with neurodevelopmental disorders and higher levels of pain and discomfort are expected in Rett syndrome, due to issues such as scoliosis, constipation, gastrointestinal problems and self-injuries. Despite this, atypical pain expressions have been reported in Rett syndrome patients that give the impression that they are not in pain (1). Impaired nociception has been directly linked to the MECP2 gene, which contributes to the modulate genes involved in nociceptive circuitry (1). Pain issues are also general concerns among children with disabilities. Reports have suggested that patients with autism spectrum are hyposensitive to different pain stimuli. This article is protected by copyright. All rights reserved.

PMID: 30216533

21. Distortion of Visuo-Motor Temporal Integration in Apraxia: Evidence From Delayed Visual Feedback Detection Tasks and Voxel-Based Lesion-Symptom Mapping.
Nobusako S, Ishibashi R, Takamura Y, Oda E, Tanigashira Y, Kouno M, Tominaga T, Ishibashi Y, Okuno H, Nobusako K, Zama T, Osumi M, Shimada S, Morioka S.

Front Neurol. 2018 Aug 27;9:709. doi: 10.3389/fneur.2018.00709. eCollection 2018.

Limb apraxia is a higher brain dysfunction that typically occurs after left hemispheric stroke and its cause cannot be explained by sensory disturbance or motor paralysis. The comparison of motor signals and visual feedback to generate errors, i.e., visuo-motor integration, is important in motor control and motor learning, which may be impaired in apraxia. However, in apraxia after stroke, it is unknown whether there is a specific deficit in visuo-motor temporal integration compared to visuo-tactile and visuo-proprioceptive temporal integration. We examined the precision of visuo-motor temporal integration and sensory-sensory (visuo-tactile and visuo-proprioception) temporal integration in apraxia after stroke by using a delayed visual feedback detection task with three different conditions (tactile, passive movement, and active movement). The delay detection threshold and the probability curve for delay detection obtained in this task were quantitative indicators of the respective temporal integration functions. In addition, we performed subtraction and voxel-based lesion-symptom mapping to identify the brain

lesions responsible for apraxia and deficits in visuo-motor temporal integration. The behavioral experiments showed that the delay detection threshold was extended and that the probability curve for delay detection was less steep in apraxic patients compared to controls (pseudo-apraxic patients and unaffected patients), only for the active movement condition, and not for the tactile and passive movement conditions. Furthermore, the severity of apraxia was significantly correlated with the delay detection threshold and the steepness of the probability curve in the active movement condition. These results indicated that multisensory (i.e., visual, tactile, and proprioception) feedback was normally temporally integrated, but motor prediction and visual feedback were not correctly temporally integrated in apraxic patients. That is, apraxic patients had difficulties with visuo -motor temporal integration. Lesion analyses revealed that both apraxia and the distortion of visuo-motor temporal integration were associated with lesions in the fronto-parietal motor network, including the left inferior parietal lobule and left inferior frontal gyrus. We suppose that damage to the left inferior fronto-parietal network could cause deficits in motor prediction for visuo-motor temporal integration, but not for sensory-sensory (visuo-tactile and visuo-proprioception) temporal integration, leading to the distortion of visuo-motor temporal integration in patients with apraxia.

PMID: 30210434

22. Robust Closed-Loop Control of a Cursor in a Person with Tetraplegia using Gaussian Process Regression.
Brandman DM, Burkhart MC, Kelemen J, Franco B, Harrison MT, Hochberg LR.

Neural Comput. 2018 Sep 14:1-23. doi: 10.1162/neco_a_01129. [Epub ahead of print]

Intracortical brain computer interfaces can enable individuals with paralysis to control external devices through voluntarily modulated brain activity. Decoding quality has been previously shown to degrade with signal nonstationarities-specifically, the changes in the statistics of the data between training and testing data sets. This includes changes to the neural tuning profiles and baseline shifts in firing rates of recorded neurons, as well as nonphysiological noise. While progress has been made toward providing long-term user control via decoder recalibration, relatively little work has been dedicated to making the decoding algorithm more resilient to signal nonstationarities. Here, we describe how principled kernel selection with gaussian process regression can be used within a Bayesian filtering framework to mitigate the effects of commonly encountered nonstationarities. Given a supervised training set of (neural features, intention to move in a direction)-pairs, we use gaussian process regression to predict the intention given the neural data. We apply kernel embedding for each neural feature with the standard radial basis function. The multiple kernels are then summed together across each neural dimension, which allows the kernel to effectively ignore large differences that occur only in a single feature. The summed kernel is used for real-time predictions of the posterior mean and variance under a gaussian process framework. The predictions are then filtered using the discriminative Kalman filter to produce an estimate of the neural intention given the history of neural data. We refer to the multiple kernel approach combined with the discriminative Kalman filter as the MK-DKF. We found that the MK-DKF decoder was more resilient to nonstationarities frequently encountered in-real world settings yet provided similar performance to the currently used Kalman decoder. These results demonstrate a method by which neural decoding can be made more resistant to nonstationarities.

PMID: 30216140

23. Human Parechovirus 3 in Infants: Expanding our Knowledge of Adverse Outcomes.
Joseph L, May M, Thomas M, Smerdon C, Tozer S, Bialasiewicz S, McKenna R, Sargent P, Kynaston A, Heney C, Clark JE.

Pediatr Infect Dis J. 2018 Sep 10. doi: 10.1097/INF.0000000000002136. [Epub ahead of print]

BACKGROUND: Human parechovirus particularly genotype 3 (HPeV3), is an emerging infection affecting predominantly young infants. The potential for neurological sequelae in a vulnerable subset is increasingly apparent. A review of two epidemics of HPeV infection in 2013 and in 2015 in Queensland, Australia was undertaken, with an emphasis on identifying adverse neurodevelopmental outcome. METHODS: All hospitalized cases with laboratory-confirmed HPeV infection between October 2013 June 2016 were identified. Clinical, demographic, laboratory and imaging data were collected and correlated with reported developmental outcome. RESULTS: Laboratory-confirmed HPeV infections were identified in 202 patients across 25 hospitals; 86.6% (n=175) were younger than 3 months 16.3% (n=33) received intensive care admission. Of 142 cerebrospinal fluid (CSF) samples which were HPeV PCR positive, all 89 isolates successfully genotyped were HPeV3. Clinical information was available for 145 children; 53.1% (n=77) had follow up from a paediatrician, of whom 14% (n=11) had neurodevelopmental sequelae, ranging from hypotonia and gross motor delay to spastic quadriplegic cerebral palsy and cortical visual impairment. Of 15 children with initially abnormal brain magnetic resonance imaging (MRI), 47% (n=7) had neurodevelopmental concerns, the remainder had normal development at follow up between 6 - 15 months of age. CONCLUSIONS: This is the largest cohort of HPeV3 cases with clinical data and paediatrician-assessed neurodevelopmental follow up to date. Developmental concerns were identified in 11 children at early follow-up. Abnormal MRI during acute

infection did not specifically predict poor neurodevelopmental in short-term follow-up. Continued follow-up of infants and further imaging correlation is needed to explore predictors of long term morbidity.

PMID: 30204658

24. Planned delivery route of preterm breech singletons and neonatal and 2-year outcomes: a population-based cohort study.
Lorthe E, Sentilhes L, Quere M, Lebeaux C, Winer N, Torchin H, Goffinet F, Delorme P, Kayem G; EPIPAGE-2 Obstetric Writing Group.

BJOG. 2018 Sep 14. doi: 10.1111/1471-0528.15466. [Epub ahead of print]

OBJECTIVE: To assess whether planned route of delivery is associated with perinatal and 2-year outcomes for preterm breech singletons. DESIGN: Prospective nationwide population-based EPIPAGE-2 cohort study. SETTING: France, 2011. SAMPLE: 390 women with breech singletons born at 26-34 weeks of gestation after preterm labor or preterm prelabor rupture of membranes. METHODS: Propensity-score analysis. MAIN OUTCOME MEASURES: Survival at discharge, survival at discharge without severe morbidity, and survival at two years of corrected age without neurosensory impairment. RESULTS: Vaginal and cesarean delivery were planned in 143 and 247 women, respectively. Neonates with planned vaginal delivery and planned cesarean delivery did not differ in survival (93.0% vs 95.7%, p=.14), survival at discharge without severe morbidity (90.4% vs 89.9%, p=.85) or survival at two years without neurosensory impairment (86.6% vs 91.6%, p=.11). After applying propensity scores and assigning inverse probability of treatment weighting, as compared with planned vaginal delivery, planned cesarean delivery was not associated with improved survival (odds ratio [OR] 1.31 [95% confidence interval [95% CI] 0.67-2.59]), survival without severe morbidity (0.75 [0.45-1.27]) or survival at two years without neurosensory impairment (1.04 [0.60-1.80]). Results were similar after matching on the propensity score. CONCLUSION: No association between planned cesarean delivery and improved outcomes for preterm breech singletons born at 26 to 34 weeks after preterm labor or preterm prelabor rupture of membranes was found. The route of delivery should be discussed with women, balancing neonatal outcomes with the higher risks of maternal morbidity associated with cesarean section performed at low gestational age. FUNDING: EPIPAGE-2 was funded by the French Institute of Public Health Research/Institute of Public Health and its partners: the French Health Ministry, the National Institute of Health and Medical Research (INSERM), the National Institute of Cancer, and the National Solidarity Fund for Autonomy (CNSA); the National Research Agency through the French EQUIPEX program of investments for the future (reference ANR-11-EQPX-0038); and the PREMUP Foundation. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. This article is protected by copyright. All rights reserved.

PMID: 30216654

25. Effect of Delayed Cord Clamping on Cerebral Oxygenation in Very Preterm Infants.
Popat H, Galea C, Evans N, Lingwood B, Colditz PB, Halliday R, Osborn D.

Neonatology. 2018 Sep 10;115(1):13-20. doi: 10.1159/000492712. [Epub ahead of print]

BACKGROUND AND OBJECTIVE: The mechanism of reported benefits of delayed cord clamping (DCC) are unclear. We aimed to determine whether DCC compared to immediate cord clamping (ICC) in very preterm infants improves cerebral oxygenation in the first 24 h. STUDY DESIGN: This is a prospective study of a subset of infants at < 30 weeks of gestation who were randomised to DCC (≥60 s) or ICC (< 10 s) and required an indwelling arterial catheter. Regional cerebral oxygenation (rScO2), blood pressure, PI, and peripheral saturation were measured and cerebral fractional tissue oxygen extraction (cFTOE) calculated for the following 3 time intervals: 3-6, 6-12, and 12-28 h of age. Functional ultrasound measures including superior vena cava flow, right ventricular output, ductus arteriosus size and shunt and anterior cerebral artery resistive index were determined. RESULTS: The mean (±SD) gestation and birth weight of the 51 study infants were 27 ± 1 weeks and 1,046 ± 241 g respectively. Twenty infants received DCC and 31 received ICC. Baseline demographics were similar between the 2 groups. Comparing DCC and ICC infants, there was no difference in rScO2 or cFTOE at any time point. Three out of 20 infants did not receive DCC due to clinical concerns. A sensitivity analysis revealed that cord clamping ≥30 s was significantly associated with increased rScO2 and decreased cFTOE at all 3 time points after adjusting for gestation. CONCLUSION: Although DCC was not associated with changes in cerebral oxygenation overall, sensitivity analysis suggested a possible effect of an increased rScO2 and a decreased cFTOE with ≥30 s of DCC.

PMID: 30199867

26. [Microcephaly].
Arroyo HA.

Medicina (B Aires). 2018;78 Suppl 2:94-100. [Article in Spanish]

Microcephaly is defined as a head circumference more than two standard deviations below the mean for gender and age. It is an important neurological sign and predictor of future disability. One of its diagnostic difficulties lies in the ranks of the head circumference reference against which we measure each child. The WHO developed growth curves that could be used universally, topic on which there may be discrepancies. Recently, Zika virus epidemic demanded to review the criteria for the diagnosis of microcephaly. The classification of the microcephaly in congenital and postnatal makes it possible to define the etiology, the associated symptoms and the prognosis. The evaluation of a child with microcephaly requires a thorough analysis of its history, clinical examination and complementary studies. MRI is the first step in the etiologic research. Genetic causes forming part of a syndrome or not, and prenatal infections are the most frequent etiologies but in half of the cases, no cause is found. The comparative hybridization genomic array (array-CGH) and full exome sequencing are techniques that more and more help us in the evaluation of patients with microcephaly. Depending on the cause and severity, children with microcephaly may have different problems such as intellectual disabilities, development retardation, epilepsy, cerebral palsy, as well as vision and hearing disorders. The microcephaly requires a multidisciplinary approach both in its initial assessment as it is its post-program monitoring.

PMID: 30199373

27. Spatiotemporal analysis of impaired microglia process movement at sites of secondary neurodegeneration post-stroke.
Kluge MG, Abdolhoseini M, Zalewska K, Ong LK, Johnson SJ, Nilsson M, Walker FR.

J Cereb Blood Flow Metab. 2018 Sep 11:271678X18797346. doi: 10.1177/0271678X18797346. [Epub ahead of print]

It has recently been identified that after motor cortex stroke, the ability of microglia processes to respond to local damage cues is lost from the thalamus, a major site of secondary neurodegeneration (SND). In this study, we combine a photothrombotic stroke model in mice, acute slice and fluorescent imaging to analyse the loss of microglia process responsiveness. The peri-infarct territories and thalamic areas of SND were investigated at time-points 3, 7, 14, 28 and 56 days after stroke. We confirmed the highly specific nature of non-responsive microglia processes to sites of SND. Non-responsiveness was at no time observed at the peri-infarct but started in the thalamus seven days post-stroke and persisted for 56 days. Loss of directed process extension is not a reflection of general functional paralysis as phagocytic function continued to increase over time. Additionally, we identified that somal P2Y12 was present on non-responsive microglia in the first two weeks after stroke but not at later time points. Finally, both classical microglia activation and loss of process extension are highly correlated with neuronal damage. Our findings highlight the importance of microglia, specifically microglia dynamic functions, to the progression of SND post-stroke, and their potential relevance as modulators or therapeutic targets during stroke recovery.

PMID: 30204044

28. Transformative journeys in childhood-onset disability with the AACPDM.
Vargus-Adams J.

Dev Med Child Neurol. 2018 Oct;60(10):967. doi: 10.1111/dmcn.13991.

PMID: 30187467

Prevention and Cure

29. Time- and sex-dependent efficacy of magnesium sulfate to prevent behavioral impairments and cerebral damage in a mouse model of cerebral palsy.
Daher I, Le Dieu-Lugon B, Lecointre M, Dupré N, Voisin C, Leroux P, Dourmap N, Gonzalez BJ, Marret S, Leroux-Nicollet I, Cleren C.

Neurobiol Dis. 2018 Sep 7. pii: S0969-9961(18)30512-6. doi: 10.1016/j.nbd.2018.08.020. [Epub ahead of print]

Cerebral lesions acquired in the perinatal period can induce cerebral palsy (CP), a multifactorial pathology leading to lifelong motor and cognitive deficits. Several risk factors, including perinatal hypoxia-ischemia (HI), can contribute to the emergence of CP in preterm infants. Currently, there is no international consensus on treatment strategies to reduce the risk of developing CP. A meta-analysis showed that magnesium sulfate (MgSO4) administration to mothers at risk of preterm delivery reduces the risk of developing CP (Crowther et al., 2017). However, only a few studies have investigated the long-term effects of MgSO4 and it is not known whether sex would influence MgSO4 efficacy. In addition, the search for potential deleterious effects is essential to enable broad use of MgSO4 in maternity wards. We used a mouse model of perinatal HI to study MgSO4 effects until adolescence, focusing on cognitive and motor functions, and on some apoptosis and inflammation markers. Perinatal HI at postnatal day 5 (P(5)) induced (1) sensorimotor deficits in pups; (2) increase in caspase-3 activity 24 h after injury; (3) production of proinflammatory cytokines from 6 h to 5 days after injury; (4) behavioral and histological alterations in adolescent mice with considerable interindividual variability. MgSO4 prevented sensorimotor alterations in pups, with the same efficacy in males and females. MgSO4 displayed anti-apoptotic and anti-inflammatory effects without deleterious side effects. Perinatal HI led to motor coordination impairments in female adolescent mice and cognitive deficits in both sexes. MgSO4 tended to prevent these motor and cognitive deficits only in females, while it prevented global brain tissue damage in both sexes. Moreover, interindividual and intersexual differences appeared regarding the lesion size and neuroprotection by MgSO4 in a region-specific manner. These differences, the partial prevention of disorders, as well as the mismatch between histological and behavioral observations mimic clinical observations. This underlines that this perinatal HI model is suitable to further analyze the mechanisms of sex-dependent perinatal lesion susceptibility and MgSO4 efficacy.

PMID: 30201311

30. Mesenchymal Stem Cells for Severe Intraventricular Hemorrhage in Preterm Infants: Phase I Dose-Escalation Clinical Trial.
Ahn SY, Chang YS, Sung SI, Park WS.

Stem Cells Transl Med. 2018 Aug 21. doi: 10.1002/sctm.17-0219. [Epub ahead of print]

We previously demonstrated that transplanting mesenchymal stem cells (MSCs) improved recovery from brain injury induced by severe intraventricular hemorrhage (IVH) in newborn rats. To assess the safety and feasibility of MSCs in preterm infants with severe IVH, we performed a phase I dose-escalation clinical trial. The first three patients received a low dose of MSCs (5 × 106 cells/kg), and the next six received a high dose (1 × 107 cells/kg). We assessed adverse outcomes, including mortality and the progress of posthemorrhagic hydrocephalus. Intraventricular transplantation of MSCs was performed in nine premature infants with mean gestational age of 26.1 ± 0.7 weeks and birth weight of 808 ± 85 g at 11.6 ± 0.9 postnatal days. Treatment with MSCs was well tolerated, and no patients showed serious adverse effects or dose-limiting toxicities attributable to MSC transplantation. There was no mortality in IVH patients receiving MSCs. Infants who underwent shunt surgery showed a higher level of interleukin (IL)-6 in cerebrospinal fluid (CSF) obtained before MSC transplantation in comparison with infants who did not receive a shunt. Levels of IL-6 and tumor necrosis factor-α in initially obtained CSF correlated significantly with baseline ventricular index. Intraventricular transplantation of allogeneic human UCB-derived MSCs into preterm infants with severe IVH is safe and feasible, and warrants a larger, and controlled, phase II study. Stem Cells Translational Medicine 2018.

PMID: 30133179