REVIEW ARTICLE

THE EVIDENCE-BASE FOR CONCEPTUAL APPROACHES AND ADDITIONAL THERAPIES TARGETING LOWER LIMB FUNCTION IN CHILDREN WITH CEREBRAL PALSY: A SYSTEMATIC REVIEW USING THE INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH AS A FRAMEWORK

Inge Franki, PT^{1,3}, Kaat Desloovere, PhD^{2,3}, Josse De Cat, PT^{2,3}, Hilde Feys, PT, PhD³, Guy Molenaers, MD, PhD^{2,4,5}, Patrick Calders, PhD¹, Guy Vanderstraeten, MD, PhD¹, Eveline Himpens, PT, PhD¹ and Christine Van den Broeck, PT, PhD¹

From the ¹Rehabilitation Sciences and Physiotherapy, Artevelde University College, Ghent University, Ghent, ²Clinical Motion Analysis Laboratory, University Hospital Pellenberg, ³Department of Rehabilitation Sciences, KU Leuven, ⁴Department of Paediatric Orthopaedics, University Hospital Pellenberg and ⁵Department of Musculoskeletal Sciences, KU Leuven, Belgium

Objective: This systematic review provides an overview of the effectiveness of conceptual approaches and additional therapies used in lower limb physical therapy of children with cerebral palsy and supports the development of clinical guidelines.

Data sources and study selection: A literature search in 5 electronic databases was performed, extracting literature published between 1995 and 2009. Studies were evaluated using the framework recommended by the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM), which classifies outcomes according to the International Classification of Functioning, Disability and Health (ICF).

Data extraction: Three evaluators rated the strength of evidence of the effects according to the AACPDM levels of evidence classification, and the quality of the studies according to the AACPDM conduct score system.

Data synthesis: A total of 37 studies used conceptual approaches (neurodevelopmental treatment (NDT), conductive education, Vojta therapy, sensory integration, functional training and goal-oriented therapy) and 21 studies focused on additional therapies (aquatic therapy and therapeutic horse-riding).

Conclusion: Level II evidence was found for the effectiveness of therapeutic horse-riding on posture and for NDT and functional training on gross motor function. Goal-oriented therapy and functional training were effective on the attainment of functional goals and participation. With level IV evidence, NDT was effective on all levels of the ICF.

Key words: cerebral palsy; physical therapy; evidence-based; ICF.

J Rehabil Med 2012; 44: 396-405

Correspondence address: Inge Franki, Rehabilitation Sciences and Physiotherapy Ghent Campus Heymans 1B3, De Pintelaan 185, 9000 Ghent, Belgium. E-mail: inge.franki@ugent.be

Submitted August 4, 2011; accepted March 20, 2012

INTRODUCTION

Cerebral palsy (CP) describes a group of disorders of movement and posture that cause activity limitations. CP is attributed to non-progressive disturbances occuring in the developing foetal or infant brain (1, 2).

The effectiveness of different basic physical therapy (PT) techniques in the treatment of children with CP has been described in a previous article (3). The results of that analysis revealed limited interaction effects between the different levels of the International Classification of Function, Disability and Health (ICF) of the World Health Organization (WHO), thereby suggesting that specific neurological approaches and motor learning strategies might be necessary to facilitate these interaction effects.

Different principles of motor learning can be recognized. Neurophysiological and neuromaturational approaches are based largely on assumptions drawn from the neuromaturational theories of development. The main assumption of these theories is that the development of movements and motor skills result solely from the neurological maturation of the central nervous system (CNS): higher centres inhibit and control lower centres, thereby allowing voluntary movement (4).

That initial theory of motor development has evolved, with more recent theories of motor learning emphasizing that motor behaviour or developing behaviours should not be viewed as the unfolding of predetermined patterns represented in the CNS. These approaches favour a more heterarchical view, in which motor development and coordination are assumed to emerge from the dynamic interaction of many subsystems in a task-specific context. These approaches, therefore, are based on an active rather than a passive view of motor learning. People learn by actively attempting to solve the problems inherent to a functional task (5, 6).

In treatment of CP, various approaches are based on different theories of motor learning. Commonly used approaches in treatment of children with CP are neurodevelopmental treatment (NDT) or Bobath therapy, conductive education (CE) by Petö, reflex locomotion therapy by Vojta, and functional task-oriented training. Other methods used are the patterning method by Doman & Delacato, and sensory integration by Ayres.

NDT or Bobath therapy (Karl & Bertha Bobath, 1943) is an interdisciplinary problem-solving approach to the assessment, treatment and management of individuals with changes in sensorimotor, perceptual and cognitive function, tone and patterns of movement resulting from a CNS lesion (7, 8). In the last decade, especially, the use of NDT in treatment of children with CP has been controversial, with the most common concern that NDT insufficiently targets functional activities and participation by using only neuromaturational strategies in learning (9).

CE (Andreas Petö, 1945) is based on an educational rather than on a medical model of intervention. CE integrates educational and rehabilitation goals into a single programme to assist children with motor dysfunction to attain orthofunction, enabling them to attend school with maximum independence (10). Repetitive learning is thereby a central aspect within CE. In the same way as for NDT, several objections have been raised against CE, and cost-effectiveness, especially, is seen as a major concern (11).

In the Vojta method (Vaclav Vojta, 1968) normal patterns of movement sequences, for example, reaching and grasping, standing up and walking, are not taught or trained as such. Vojta therapy rather stimulates the brain, activating "innate, stored movement patterns", which are then "exported" as coordinated movements involving the musculature of the trunk and extremities (12).

Functional and task-oriented training (5, 6) are based on learning motor abilities that are meaningful in the child's environment and perceived as problematic by either the child or the parents. The child has an active role in finding solutions to motor problems rather than the physical therapist providing a solution using handling. Functional goals are established with parents and children based on their priorities and functional activities are assumed to be learned by repetitive practice of goal-related tasks in functional situations (5, 6).

A closely related approach is the method of individual goal setting, as proposed by Bower et al. (13). Like functional and task-oriented training, this strategy uses the identification of individually defined tailor-made goals to structure the therapy process (13). However, the approach is not necessarily based on repetitive learning, but sometimes uses an eclectic approach or a mixture of different techniques.

The patterning method (Doman & Delacato, 1955) derives from a phylogenetic interpretation of development. The therapeutic programme aims to recapitulate the physiological stages of motor development through exercises, by the involuntary imposition of patterns of activation or by having the child voluntarily practice, presumably missed, earlier stages of mastery (14).

Sensory integration (Jean Ayres, 1960) refers to a theory and a neurological process that enables the individual to take in, interpret, integrate and use the spatio-temporal aspects of sensory integration from the body and the environment to plan and produce organized behaviour. It postulates that learning is dependent on the ability of normal children to take in sensory information derived from the environment and from movement of their bodies, to process and integrate these sensory inputs within the CNS and to use this sensory information to plan and produce organized behaviour (15).

Besides these conceptual approaches, therapeutic horseriding or hippotherapy and aquatic therapy or hydrotherapy are frequently used additional therapies for children with CP, with many different opinions regarding their effectiveness (16–18).

Despite the frequent use of these treatment strategies, the effectiveness of these interventions is not clear and, especially, effectiveness on the different levels of the ICF has not been elucidated. Little consistency is provided on the use of these different approaches in clinical practice of lower limb treatment in CP. However, a differentiation of the effects supports a targeted treatment approach based on an adequate selection of intervention type adjusted to the specific therapy goal.

This systematic review aims to summarize the effectiveness of different conceptual approaches and additional therapies used in children with CP and to differentiate the outcome effects on the different levels of the ICF. It thereby aims to identify interaction effects between the different outcome levels of the ICF and to explore the possibilities of developing clinical guidelines in PT treatment of children with CP.

METHODS

Search strategy

A systematic, stepwise search of the literature on PT in CP was performed using the following electronic databases: Web of Science, PubMed, Cochrane Library, Physiotherapy Evidence Database (PEDro) and CINAHL. General search terms used were: "cerebral palsy" and "physiotherapy", "physical therapy", "exercise", and "training". More specific search terms were: "functional training", "functional therapy", "neurodevelopmental treatment", "Bobath", "Petö", "conductive herapy", "conductive education", "Vojta", "reflex locomotion", "patterning", "doman delacato", "sensory integration", "hydrotherapy", "aquatic therapy", "hippotherapy", "horse-riding" and "goal-setting".

Inclusion criteria were: original articles published in peer-reviewed journals between January 1995 and December 2009, focusing on PT interventions targeting lower limb and trunk treatment in children and adolescents (<18 years) with CP. Only articles written in English were included. Articles including children with different pathologies or only targeting the upper limb were excluded from the study, as were interventions using mixed approaches or techniques.

Based on the title and abstracts of the articles, a first selection resulted in 127 articles. All articles were subsequently screened by the first author. Articles not meeting the inclusion criteria were withheld. If the title and abstract did not provide sufficient information to fulfil the inclusion criteria, the full article was checked. In addition, all case studies, expert opinions and non-systematic reviews were excluded. As a final step, the reference lists of all systematic reviews included in the study were searched, and missing articles meeting the inclusion criteria were added. The inclusion of doubtful articles was discussed with a second and third assessor.

398 I. Franki et al.

A resulting total of 58 studies was included in the study. A flow diagram of the selection process is shown in Fig 1.

Data collection

The full text of all selected articles was read. The following data were extracted: type of intervention, numbers of patients included, topographic distribution of cerebral palsy, age of patients, type, frequency and duration of intervention, duration of follow-up, evaluation method and timing, summary of the results, and conclusion.

Grouping data

The selected articles were subdivided into two categories: a first group of articles covering the conceptual PT approaches (n=37), and a second group of articles focusing on additional therapies (n=21).

Classification and rating of the different outcome measures

Classification of outcome measures, rating of the level of evidence and scoring of conduct scores was carried out by 3 independent evaluators: 1 PhD physical therapist (CVdB), 1 research physical therapist (IF) and 1 physical therapist MSc student (CD).

Classification of the outcome

The evaluators classified the outcome of the intervention on the level of the ICF model: body structure and function, activities and participation, personal factors and environmental factors.

Body structures are defined as the anatomical parts of the body, such as organs, limbs and their components. *Body functions* are the physiological functions of body systems (including psychological functions). *Activity* is the execution of a task or action by an individual. *Participation* is involvement in a life situation. *Environmental factors* make up the physical, social and attitudinal environment in which people live and conduct their lives. They can be viewed as facilitators (positive influence) or barriers (negative influence). *Personal factors* are the particular background of an individual's life and living and comprise features of the individual that are not part of a health condition. These factors may include gender, race, age and other health conditions (19).



Fig. 1. Selection process.

Level of evidence

The same 3 independent evaluators rated the studies according to their level of evidence using the rating system proposed by the American Academy of Cerebral Palsy and Developmental Medicine (AACPDM) (20). Level of evidence describes the potential in a research study design to control for factors, other than the intervention, that may affect the observed outcome. In descending order, the levels of evidence decreasingly demonstrates that the intervention, and not something else, is responsible for the observed outcome. Level I evidence is the most definitive for establishing causality, with greatest reduction in bias. Level IV evidence can only hint at causality; level V evidence only suggests the possibility (20). Any discrepancies were discussed and a final agreement score was used.

In a first step, agreement between the grading of the levels of evidence assigned by the different evaluators was tested in pairs, using a Kappa coefficient. The resulting agreement scores varied between 0.604 and 0.780.

As a second step, all discrepancies were discussed. The raters argued the reasons for the score given. If an agreement could not be found in this way, the score with the highest frequency was chosen (2 out of 3 raters scoring the same level of evidence). This final consensus score was used in the summary tables.

Quality of the studies

The conduct of the study rating indicates the extent to which a study applied the control possible within the research design. Quality assessment was performed using the conduct score system proposed by the AACPDM (20). For group designs, the conduct of an individual study is judged as "strong" (yes on 6–7 questions), "moderate" (score 4–5) or weak (\leq 3). For single subject designs, the conduct of an individual study is judged as "strong" (yes on 11–14 questions), moderate (score 7–10) or weak (score <7). Systematic reviews are also evaluated using a score system, reaching a maximum of 10 points. Validity assessment of the studies was performed by 3 independent evaluators. Similarly to the quality rating score, larger discrepancies were discussed and an agreement score was used. Inter-rater reliability of the validity assessment system was tested, resulting in an Intraclass Correlation Coefficient (ICC) score of 0.927 for group designs, 0.947 for single subject designs, and 0.906 for systematic reviews.

Similarly to the quality rating score, larger discrepancies were discussed. The answers of the different assessors to the questions were compared and the questions causing the disagreement were traced. Again, the reasons for the scores given was discussed until an agreement was found and if no consensus could be found, the score with the highest frequency was chosen. After this discussion, the conduct score was recalculated.

These consensus scores were used in the results tables.

RESULTS

Conceptual physical therapy approaches

Within the category of conceptual approaches, the included articles were grouped according to their named approach: Bobath or NDT (n=13), Vojta or reflex locomotion therapy (n=1), Petö or CE (n=13), Doman Delacato or patterning (n=0), a goal-oriented approach (n=3), functional training (n=6) and sensory integration according to Ayres theory (n=1).

Neurodevelopmental treatment or Bobath therapy

Eleven intervention studies, which included a total of 181 children with CP, evaluated the effect of NDT Table SI (available from https://doi.org/10.2340/16501977-0984) (21–23).

Five studies used a single-subject research design (SSRD), 3 studies were case series and 3 studies used a randomized control trial (RCT) design. The conduct scores thereby varied between weak (n=2), moderate (n=7) and strong (n=2). The mean duration of the NDT treatment was 18.0 weeks (standard deviation (SD) 16.5 weeks) with an mean frequency of 4 times per week.

No level II evidence was found for the effectiveness of NDT on the level of *Body structure and function*. Level IV evidence was found on posture (22), spasticity (25), range of motion (ROM) (25) and mechanical efficiency (29).

On *Activity level*, level II and III evidence was found for the effectiveness of NDT on gross motor function (26–28). Two other level II studies could not find significant effects on gross motor function: one study focused on treatment contexts (21) and one study on the frequency of intervention (28). In these studies, however, significant improvements in gross motor function were registered in the intervention group (withingroup differences), but no significant between-group differences were found when compared with the control group.

One level III (26) study found significant effects on *Participation* and this on self-care and care-giver assistance.

It should be noted that many of the studies were RCTs comparing different interventions, using NDT as a control intervention. Therefore, the results of these studies could not be scored as level II evidence and had to be scored as level IV evidence. Kerem (25) compared a group of children receiving frequent NDT combined with Johnstone pressure splints (JPS) with a group of children receiving only NDT, and found a significantly higher improvement in ROM and spasticity in the combination group. A high-quality RCT by Bar-Haim (29) compared a group of children receiving Adeli Suit with a group of children receiving NDT. The results demonstrated a superior effect of Adeli Suit treatment on mechanical efficiency during activities, while no differences were found when evaluated on activity level using the Gross Motor Function Measure (GMFM). In a complex SSRD comparing an AAB with an ABA design, Cherng (30) compared the effectiveness of a NDT programme with a combined programme of NDT and body weight supported treadmill training. The results of this study demonstrated no significant effects on gait parameters or gross motor function after the periods of only NDT.

Trahan & Malouin (27), Tsorlakis (28) and Christiansen (31) all focused on frequency of intervention. Where Tsorlakis underlined the importance of an intensive treatment regime of 5 times per week (28), Trahan & Malouin and Christansen supported the feasible option of using intermittent periods with lower treatment frequencies. Both researchers demonstrated only a limited deterioration in gross motor function during these periods (27, 31).

There have been two previous systematic reviews evaluating the effectiveness of NDT in children with CP, which concluded that there was insufficient evidence to support NDT at the time of their review. Both reported the problems of evaluating and interpreting research results due to marked standardization problems in therapy, clinical and environment aspects (32, 33). The interventions evaluated by Butler & Darrah (32) and Brown & Burns were much older, and therefore there was only a limited overlap of 1 and 3 studies, respectively, with our review.

Conductive education according to Petö

Ten intervention studies evaluated the effectiveness of CE, including two RCTs and 8 case series and non-randomized controlled trials (Table SII (available from https://doi. org/10.2340/16501977-0984)) (10, 34–45). A total of 185 children with CP were included in the intervention studies. The duration of the interventions was relatively long, with a mean of 30.1 weeks (SD 46.9) and high frequency of intervention of 4.6 times per week (SD 0.42). It was remarkable that 8 of the 10 interventions demonstrated weak conduct scores.

No level II evidence was found for the effectiveness of CE.

On *Body function and structure*, the effectiveness of CE was only demonstrated with level IV evidence on language skills (37).

On *Activity level*, the effectiveness of CE was demonstrated with level IV evidence on gross motor skills and individual motor goals (36, 40, 44). Conflicting level IV evidence was available on *Participation* (36, 38, 40, 42) as well as on *Environmental factors* parental coping and stress (34, 35, 38, 40).

The systematic reviews evaluating CE concluded positive effects of CE on motor function of children with CP, with effects comparable to the effects of different treatment approaches (10, 44, 45). Training in a group probably had a significant social impact.

Sensory integration according to Ayers

One study was found evaluating the effectiveness of sensory integration (SI) in children with CP (15) (Table SIII (available from https://doi.org/10.2340/16501977-0984)).

This study, based on a RCT, compared the effectiveness of sensory training, vestibular training, balance and postural reactions, bimanual activities and motor planning with the effectiveness of a home-based training programme. Effects were evaluated on *Impairment and Activity* level using the Ayers Southern Californian Sensory Integration test and on *Activity level* using the Physical Ability Test. The results revealed significantly positive effects in favour of the children receiving sensory integration programme on both levels. Although this study had a level II design (RCT), the conduct score of this study was rated as "weak". In addition, the study statistics were limited to within-group effect sizes.

Reflex locomotion therapy or Vojta therapy

One level II study evaluated the effectiveness of reflex locomotion according to Vojta (46) (Table SIII (available from https:// doi.org/10.2340/16501977-0984)) and this only on *Activity level*. Kanda evaluated a group of 5 children with CP receiving intensive Vojta therapy for 52 months. Comparing this group of children with 2 children receiving no therapy and 3 children receiving insufficient therapy, revealed a significantly 400 I. Franki et al.

higher motor development level in the children following Vojta therapy. Taking into account the low quality (conduct score of 2/7) and the small number of participants in this study, no conclusions can be drawn on the effectiveness of Vojta therapy.

Patterning according to Doman Delacato

No study was found evaluating the effectiveness of patterning according to Delacato in children with CP.

Functional and task-oriented training

Six studies, including a total of 85 children, evaluated the effect of functional and task-oriented training, which mostly consisted of group training targeting specific activities of daily life (4, 5, 47–50) (Table SIV (available from https://doi. org/10.2340/16501977-0984)). These programmes were task-specific, with more attention on successful accomplishment of the specific tasks rather than quality of movement. Most of the studies used a variety of functional exercises and 1 study used a coordination dynamics board (47).

On *Body structure and function*, only weak evidence (level IV) was found for ROM, spasticity, and selective muscle activation (50). No significant level II effects were found on strength. Effects of the functional training programmes were mainly found on *Activity level*, with level II evidence on gross motor function and on different functional ambulation tests (5, 48, 49). One level IV and 1 level II study reported improved *Participation* measured by Pediatric Evaluation of Disability Inventory (PEDI) self-care and mobility scores (5, 6).

The mean duration of training was 21.8 weeks (SD 23 weeks). Three studies included a follow-up, with a mean follow-up period of 10.3 weeks. The intensity of treatment ranged from very intense (2 times per day) to 3 times per month.

Goal-oriented approach

Three studies evaluated the effect of a goal-oriented approach in in total of 72 children with CP (Table SV (available from https://doi.org/10.2340/16501977-0984)) (13, 51, 52). Setting goals involves identifying and formulating standards of motor activity that are in advance of the child's current capacity or which slow down deterioration. Therefore, goals need to be formulated in such a way that there is no doubt about the extent to which they have been achieved when performance is reviewed (13). In two RCTs (level II), Bower (13, 51) compared the effect of therapy based on specific and SMART (Specific, Measurable, Attainable, Realistic and Timely) formulated goals with therapy based on general aims. Significant effects were thereby highlighted on Activity level, with a positive effect on motor development evaluated by GMFM, but only in the short term. A more recent study by Löwing (52) compared goal-directed functional therapy with activity-focused therapy. This study demonstrated significantly clearer gains both on Activity (gross motor function) and Participation (measured with the PEDI) in the group of children receiving goal-directed functional therapy.

Additional therapies

Within the category of additional therapies, a subdivision was made in a group of therapies using exercises in water (hydrotherapy, aquatic exercise) (n=4) and horseback riding (therapeutic horseback riding, hippotherapy) (n=14).

Aquatic therapy or hydrotherapy

Four studies evaluated the effect of different aquatic therapy interventions in 66 children with CP, varying from swimming training sessions to individual aquatic exercises (Table SVI (available from https://doi.org/10.2340/16501977-0984)) (53–56). The mean duration of the aquatic training programmes was 17.5 weeks (SD 1.91), with a mean frequency of 2.75 times per week. Three studies used a RCT design; however, they were rated with very weak conduct scores (53, 54, 56). On the other hand, the single subject design was rated with a moderate conduct score (55).

On *Body structure and function*, level II effectiveness was demonstrated on vital capacity after 26 weeks of swimming sessions (53). Nevertheless, this study was rated as weak, based on the conduct score. Furthermore, positive effects of aquatic therapy were demonstrated on self-perception, body awareness and child behaviour (54, 56). On *Activity level*, level IV evidence was demonstrated as significantly improved water-orientation skills, improved functional mobility and gross motor function (53, 56).

Therapeutic horse-riding or hippotherapy

Fourteen intervention studies including 217 children evaluated the effectiveness of hippotherapy in children with CP (Table SVII–VIII (available from https://doi.org/10.2340/16501977-0984)) (57–73). The mean duration of therapy was 12.8 weeks (SD 5.7 weeks) with 4 studies, including a follow-up period of a mean duration of 11 weeks.

Four RCTs, 5 case series and non-randomized controlled trials and 5 single-subject designs were selected. The majority of the studies had moderate conduct scores.

On *Body structure and function*, level II evidence was demonstrated on trunk and pelvic posture and stability (58, 63) and child behaviour (57). Level IV evidence confirmed improved posture (60, 61, 67) and controversial effects on spasticity (64, 66).

On *Activities*, level II evidence was only demonstrated on upper limb function (57). In addition, 4 level IV studies demonstrated significant improvements on gross motor function (59, 62, 64, 65).

One level II study (69) could not find a statistically significant increase in *Participation*, controversial findings were found in the 2 III–IV studies (61, 65).

One level II study showed improvement in *Quality of Life* (QoL), but the results were not statistically significant (69).

The results did not concur with the findings of the 3 systematic reviews on horse-riding therapy, which concluded that evidence is available for the effectiveness of horse-riding therapy on muscle tone of children with CP. Our review found that therapeutic horse-riding was more effective to increase trunk and pelvic control and, to a lesser extent, to improve gross motor function (71–73).

Summary

Table I provides an overview of the evidence of the different interventions. For this summary table, the most commonly used outcome parameters on the different levels of the ICF were selected. Similar as in the review describing basic techniques, Table I considers the results of level II studies not statistically analysing between-group differences as level IV evidence.

On the level of body function and structure, Table I demonstrates that level II evidence was only obvious for the effectiveness of horse-riding therapy on different measures of posture and postural control and for aquatic therapy on lung function.

No effectiveness could be demonstrated on muscle strength or muscle cross-sectional area for the different interventions. An indication of the effectiveness was demonstrated by the level IV studies highlighting significant effects of therapeutic horse-riding on spasticity and energy expenditure.

On activity level, NDT, functional training, goal-oriented approach, sensory integration as well as Vojta therapy significantly influenced gross motor function and this was graded as level II evidence. However, the effectiveness of sensory integration and Vojta therapy was only evaluated in one study, both with a low conduct score, indicating careful consideration of these results. The effectiveness of CE, therapeutic horse-riding and aquatic therapy on gross motor function was only supported by level IV evidence. NDT was the only intervention that significantly improved different gait measures; however, these only reached level IV evidence.

Of all the studies, 16 used different participation outcome measures. Only two level II studies found significant effects on participation, including one level II study indicating significant effects of goal-directed therapy on social function measured using the PEDI (62). The effectiveness of NDT on self-care skills, caregiver assistance and subjective findings by the parents was demonstrated with level IV evidence (21).

DISCUSSION

This systematic review overviews the effectiveness of different conceptual approaches and additional therapies used in PT of children with CP. A total of 52 articles were included in this analysis. Thirty-four included articles were graded as level II, 3 as level III, and 21 as level IV. As for the basic techniques, these numbers demonstrate that high-quality research in PT is possible and is being done. However, the validity assessment

Table I. Overview of the number of studies demonstrating level II, III and IV evidence

Level II evidence			
Body structure and function	Spasticity	<i>Posture</i> Therapeutic horse-riding, 2/3 (57, 58 , 63)	Energy expenditure/movement efficiency
	ROM	Strength	Muscle morphology/cross sect area
		Functional training, 0/1 (48)	
Activity and participation	Gait	Gross motor function	Participation
	Functional training, 1/2 (48 , 49)	NDT, 2/4 (27, 28, 29, 31)	Goal-oriented approach, 1/1 (52)
		Goal-oriented approach, $3/3$ (13, 61, 62)	Functional training, $1/1$ (5)
		Functional training, $2/3$ (5, 48, 49) Conductive education $0/2$ (37, 39)	Environmental factors
		Therapeutic horse-riding $0/2$ (57, 69)	Conductive education, $0/1$ (37)
		Vojta therapy, 1/1 (46)	Quality of Life
			Therapeutic horse-riding, 0/1 (69)
Level III and IV evidence			
Body structure and function	Spasticity	Posture	Energy expenditure/movement efficiency
	Therapeutic horse-riding, 1/2	NDT, 1/1 (22)	Therapeutic horse-riding, 1/1 (59)
	(64, 68)	Therapeutic horse-riding, 3/3 (60, 61, 67)	NDT, 1/1 (29)
	ND1, 1/2 (25 , 30) Eunctional training 1/1 (40)		Aquatic therapy, 0/1 (55)
	ROM	Strongth	Muscle morphology/cross-sectional area
	NDT. 1/1 (20)	Aquatic therapy. 0/1 (55)	wasele morphology/cross sectional area
	Functional training, 1/1 (50)	1	
Activity and participation	Gait	Gross motor function	Participation
	NDT, 2/2 (24, 30)	NDT, 4/4 (24, 26, 29, 30)	NDT, 1/1 (26)
	Functional training, 2/2 (48, 49)	Conductive education, 3/4 (36 , 40 , 41,	Functional training, 1/1 (6)
	Aquatic therapy, 0/1 (55)	42)	Conductive education, $2/4$ (36, 38 , 40 ,
		Functional training, $3/4$ (6, 48, 49, 50)	42) Therementia here riding $1/2$ (61, 65)
		Therapeutic horse-riding 5/6 (59 61 62	Environmental factors
		64, 65, 68)	Conductive education, 1/4 (34, 35, 38,
		Sensory integration, 1/1 (15)	40)

.../... indicates the number of studies reaching significant treatment effects vs the total number of studies evaluating the effect of the intervention on that specific parameter. In case of conflicting evidence, the references demonstrating significant effects are bold. ROM: range of motion; NDT: neurodevelopmental treatment.

demonstrates an overweight of moderate and weak conduct scores, highlighting limitations in methodological conduct, such as appropriate statistical or visual analysis and description of the control groups. In addition, the number of individuals overall who have been studies is small.

Kappa coefficients for the level of evidence scores were similar to the agreement scores reported in the previous article summarizing basic techniques and were acceptable (3). The ICC scores calculated for the conduct scores system, however, were much higher in this part of the systematic review (0.927 for group designs, 0.947 for SSRDs and 0.906 for systematic reviews) as in the part evaluating basic techniques (3) (0.640 for group designs, 0.352 for single subject designs and 0.888 for systematic reviews). This may be explained by the experience of the raters, who scored and discussed the articles described in the previous article first. To increase inter-rater reliability of the scores, appropriate training and experience in training might therefore be recommendable.

No adverse effects were demonstrated in any of the studies.

As for the individual techniques, summarizing the effectiveness of all interventions demonstrates that the ICF provides a good model to evaluate the effectiveness of different physiotherapy interventions for CP. As recognized in the systematic review describing basic techniques (3), only specific measurements of QoL could not be scored by the ICF (3). In clinical research trials, however, limited interventions measure outcome effects on all levels of the ICF and again, especially older studies only evaluated effectiveness on the level of body structure and function.

Only the studies using NDT appear to demonstrate a tendency of effectiveness on all levels of the ICF: impairment, activity and, to a lesser extent, participation measures, although the results were inconsistent. Surprisingly, in contrast to the recent critiques of NDT being too passive and not sufficiently targeting activity and participation level, 2 level II (27, 28), 1 level III (26) and 3 level IV studies (23, 24, 30) highlight a significant effect on gross motor function. These studies demonstrate the recent developments within the neurodevelopmental treatment concept, with an obvious and important component of integration of improved muscle tone and length into function. The results refute the arguments that NDT only targets problems at impairment level without sufficient attention to activity level and functionality of the child. From a motor learning point of view, PT in an NDT context is considered not to be a repetition of the functional task, but is carefully considered by task-analysis. In other words, the child is not taught to do these skills as best he or she can despite the presence of spasticity or fluctuating tone. Rather, there is specific preparation for specific functional skills to enable the child to function in the most efficient way possible. The aim is to perform postural and voluntary tasks with the least possible interference from abnormal postural tone.

The results of this review are not confirmed by the conclusions of the two high-quality systematic reviews by Butler & Darrah (32) and Brown & Burns (33), evaluating the effectiveness of NDT. Butler (27) and Brown (28) did not include the same studies in their analysis. The studies in their reviews were much older (pre-2001) and therefore, there was a limited overlap of 1 and 3 studies, respectively, with this review. In addition, the interventions available for their reviews were of lower quality.

CE claims to increase orthofunction, which means that, in spite of fundamental motor problems, an individual acquires strategies to be as independent as possible in activities of daily living and lives as normally as possible. Thus, CE is expected to be an intervention at the activity and participation dimensions of the ICF. Indeed, regarding CE, level IV evidence was demonstrated only on gross motor function, No studies evaluated the effectiveness of CE on body structure and function parameters, such as strength, ROM and spasticity, but only on cognition and language development.

From a motor learning perspective, the repetitive learning principles from CE lean to a certain extent towards the functional and task-oriented approach. It is possible that the additional impact of the goal-setting procedures and the active learning component in the functional and task-oriented approach, have a clearer and more obvious impact on gross motor function and participation.

The results of the goal-oriented approach by Bower et al. (13, 51) and the functional and task-oriented approaches (5, 6, 6)50) demonstrate that individual goal-setting procedures can be very effective on the attainment of individual functional goals and gross motor function. Most of the individual goals are only defined on activity level. In the short term especially, the definition of measurable, specific treatment goals can be very motivating for therapist, parents and children. On participation level, only Ahl et al. (6), Ketelaar et al. (5) and Löwing et al. (52) found significant effect of task-oriented training on the PEDI, but no other measures of participation, such as Children's Assessment of Participitation and Enjoyment or Assessment of Life Habits for Children were used. However, in the Measures of Process Care Questionnaire, parents reported positive feelings about their involvement in the therapy and the goal-setting process, suggesting a positive impact on the child's environment (6, 51).

These approaches use a more neuromaturational learning component, and, therefore, Vojta therapy especially would be expected to work in the body structure and function dimension of the ICF. Nevertheless, there were no measures in this dimension. The 1 outcome of statistically significant gross motor function score in the activity dimension may represent greater coordination of purposeful movement.

It would be interesting and useful to compare the effectiveness of these more "passive forms" of learning with the more recent "action" approaches. Ketelaar et al. (5) compared a functional task-oriented approach with an approach that was based more on normalization of quality of movement, like that of NDT. The major difference between both approaches was defined as the active learning component. Normalization of quality of movement, however, might not necessarily mean a passive learning component, but may also be learned in an active way and in a functional, task-oriented context. In this regard, another important aspect that needs more detailed investigation is age and severity of involvement. Children who are more mildly involved might benefit from a different approach from those children with severe involvement and, maybe, young children would also benefit from another approach than older children.

Home-based training was not included, since these programmes often include a mixture of approaches and techniques, and a mixture of occupational therapy and physical therapy. However, the authors would like to state that this does not mean that they underestimate the value of home-based therapy. As demonstrated by Karnish et al. (21), children with disabilities have been found to demonstrate superior performance of skills in natural educational settings compared with in an isolated therapy room.

A recent approach that could unfortunately not be included this review, is context therapy, as proposed by Darrah et al. (74) and Law et al. (75). This approach is also built on the theoretical construct of dynamical systems theory, which posits that motor behaviours are organized around functional tasks or goals and that the specific motor solution is influenced by the spontaneous interaction between variables from the child, the task and the environmental influences. Context therapy emphasizes changing the parameters of the task or environment rather than focusing on remediation of a child's abilities. The assumption of this approach is that changes in the task and/or environment will enable the child to perform an activity that they were unable to do previously.

This is a review of the research evidence for the effectiveness of the most commonly used therapy approaches as a first step in supporting the therapist to build an evidence-based targeted therapy programme based on the main problems of the child. It is based on the AACPDM review process, which uses the ICF as a twp-part conceptual framework: the ICF to identify the types of evidence currently available, and a level of evidence classification to rate the strength of that evidence. The types of outcomes that have been studied so far are very few; outcomes for which we have positive evidence have not yet been adequately replicated. The robustness of the evidence is still too weak and the number of peadiatric studies is still too few to provide conclusive evidence. Therefore, it is still very early to define specific clinical guidelines. However, a targeted treatment approach based on appropriate evaluation of all levels of the ICF is advised to create an appropriate, individually-defined treatment plan. Integrating improvements at body function and structure during functional activities and vice versa appears to be very challenging for children with CP. Therefore, continuing high-quality research focusing on the motor-learning aspect of integrating these components remains necessary for future research.

CONCLUSION

- The effects of NDT are demonstrated at all levels of the ICF.
- The use of CE has significant effects on gross motor function.
- Setting individual, measurable goals supports the achievement of functional PT goals.

- Functional training can be beneficial in learning new motor activities, but no studies demonstrate benefit on the level of body function and structure.
- Hippotherapy can be considered as an effective additional therapy method to improve posture and postural control.
- Except for a beneficial impact on lung function, hydrotherapy is not yet proven to be effective in children with CP.

ACKNOWLEDGEMENTS

The authors wish to acknowledge with gratitude Professor Dr F. Cools for his methodological support and Cathy Duchateau for her valuable contribution to the scoring of the selected articles.

REFERENCES

- Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl 2007; 109: 8–14.
- Cans C, Dolk H, Platt MJ, Colver A, Prasauskiene A, Kraegeloh-Mann I. Recommendations from the SCPE collaborative group for defining and classifying cerebral palsy. Dev Med Child Neurol 2007; 49: 35–38.
- Franki I, Desloovere K, De Cat J, Feys H, Molenaers G, Calders P, et al. The evidence-base for basic physical therapy techniques targeting lower limb function in children with cerebral palsy: a systematic review using the ICF as a framework. J Rehabil Med 2012; 44: 385–395.
- Shumway-Cook A, Woollacott MH. Motor control: theory and practical applications. Baltimore, MD: Williams & Wilkins; 1995.
- Ketelaar M, Vermeer A, Hart H, Van Petegem-van Beek E, Helders P. Effects of a functional therapy program on motor abilities of children with CP. Phys Ther 2001; 81: 1535–1545.
- Ahl LE, Johansson E, Granat T, Brogren Carlberg E. Functional therapy for children with CP: an ecological approach. Dev Med Child Neurol 2005; 47: 613–619.
- Raine S. The current theoretical assumptions of the Bobath concept as determined by the members of the BBTA. Phys Ther Pract 2007; 3: 137–152.
- International Bobath Instructors Training Association. Theoretical assumptions [Internet]. [Accessed 7 April 2009]. Available from: http://www.ibita.org.
- Damiano DJ. Physiotherapy management in cerebral palsy: moving beyond philosophies. In: Scrutton D, Damiano DJ, Mayston MJ, editors. Management of the motor disorders of cerebral palsy. 2nd edn. London: MacKeith Press; 2004, p. 161–169.
- Darrah J, Watkins B, Chen L, Bonin C. Conductive education intervention for children with CP: an AACPDM evidence report. Dev Med Child Neurol 2004; 46: 187–203.
- Kozma I, Balogh E. A brief introduction to conductive education and its application at an early age. Infants Young Children 1995; 8: 68–74.
- Vojta V. The basic elements of treatment according to Vojta. In: Scrutton. Management of the motor disorders of children with cerebral palsy. Suffolk: Lavenham Press Ltd; 1984, p. 75–89.
- Bower E, McLellan DL, Arney J, Campbell MJ. A randomised controlled trial of different intensities of physiotherapy and different goal-setting procedures in 44 children with cerebral palsy. Dev Med Child Neurol 1996; 38: 226–237.
- Cohen HJ, Birch GH, Taft LT. Some considerations for evaluating the Doman-Delacato "patterning" method. Pediatrics 1970; 45: 302–315.
- 15. Bumin G, Kayihan H. Effectiveness of two different sensoryintegration programmes for children with cerebral palsy. Disabil

Rehabil 2001; 23: 394-399.

- Anttila H, Suoranta J, Malmivaara A, Mäkelä M, Autti-Rämö I. Effectiveness of physiotherapy and conductive education interventions in children with cerebral palsy: a focused review. Am J Phys Med Rehabil 2008; 87: 478–501.
- 17. Hur JJ. Review of research on therapeutic interventions for children with cerebral palsy. Acta Neurol Scand 1995; 91: 423–432.
- Kunz R, Autti-Rämo I, Anttila H, Malmivaara A, Mäkela M. A systematic review finds that methodological quality is better than its reputation but can be improved in physiotherapy trials in childhood cerebral palsy. J Clin Epidemiol 2006; 59: 1239–1248.
- International Classification of Functioning, Disability and Health

 Children and Youth Version. ICF-CY. Geneva: World Health
 Organization; 2007.
- Darrah J, Hickman R, O'Donnell M, Vogtle L, Wiart L. AACPDM methodology to develop systematic reviews of treatment interventions (Revision 1.2) 2008 version [Internet]. Availble from: www. aacpdm.org.
- Karnish K, Bruder MB, Rainforth B. A comparison of physical therapy in two school based treatment contexts... an isolated therapy room or a natural educational setting. Phys Occup Ther in Ped 1995; 15: 1–25.
- Jonsdottir J, Fetters L, Kluzik J. Effects of physical therapy on postural control in children with cerebral palsy. Ped Phys Ther 1997; 9: 68–75.
- Trahan J, Malouin F. Changes in the gross motor function measure in children with different types of CP: an eight months follow-up study. Ped Phys Ther 1999; 11: 12–17.
- Adams A, Chandler L, Schuhmann K. Gait changes in children with CP following a neurodevelopmental treatment course. Ped Phys Ther 2000; 12: 114–120.
- 25. Kerem M, Livanelioglu A, Topcu M. Effects of Johnstone pressure splints combined with neurodevelopmental therapy on spasticity and cutaneous sensory inputs in spastic cerebral palsy. Dev Med Child Neurol 2001; 43: 307–313.
- 26. Knox V, Evans AL. Evaluation of the functional effects of a course of Bobath therapy in children with CP: a preliminary study. Dev Med Child Neurol 2002; 44: 447–460.
- Trahan J, Malouin F. Intermittent intensive physiotherapy in children with CP: a pilot study. Dev Med Child Neurol 2002; 44: 233–239.
- Tsorlakis N, Evaggelinou C, Grouios G, Tsorbatzoudis. Effect of intensive neurodevelopmental treatment in gross motor function of children with CP. Dev Med Child Neurol 2004; 46: 740–745.
- Bar-haim S, Harries N, Belokopytov M, Frank A, Copeliovitch L, Kaplanski J, et al. Comparison of efficacy of Adeli suit and neurodevelopmental treatments in children with cerebral palsy. Dev Med Child Neurol 2006; 48: 325–330.
- Cherng RJ, Liu CF, Lau TW, Hong RB. Effect of treadmill training with body weight support on gait and gross motor function in children with spastic cerebral palsy. Am J Phys Med Rehab 2007; 86: 548–555.
- Christansen. Intermittent versus continuous physiotherapy in children with cerebral palsy. Dev Med Child Neurol 2008; 50: 290–293.
- Butler C, Darrah J. Effects of Neurodevelopment treatment (NDT) for CP: an AACPDM evidence report. Dev Med Child Neurol 2001; 43: 778–790.
- Brown T, Burns S. The efficacy of neurodevelopmental treatment in paediatrics: a systematic Review. Br J Occup Ther 2001 64: 235–244.
- 34. Coleman GJ, King JA, Reddihough DS. A pilot evaluation of conductive education based intervention for children with cerebral palsy: the Tongala project. J Paed Child Health 1995; 31: 412–417.
- 35. Catanese AA, Coleman GJ, Reddihough DS. Evaluation of an early childhood program based on principles of conductive education – the Yooralla project. J Paed Child Health 1995; 41: 418–422.
- 36. Hurr JJA. Skills for independence for children with cerebral palsy:

J Rehabil Med 44

a longitudinal study. Int J Dev Educ 1997; 44: 263-274.

- Reddihough DS, King J, Coleman G, Catanese T. Efficacy of programmes based on conductive education for young children with cerebral palsy. Dev Med Child Neurol 1998; 40: 763–770.
- 38. Woolfson LH. Using a model of transactional developmental regulation to evaluate the effectiveness of an early intervention programme for pre-school children with motor impairments. Child Care Health Dev 1999; 25: 55–79.
- Stiller C, Marcoux BC, Olson RE. The effect of conductive education, intensive therapy, and special education services on motor skills in children with cerebral palsy. Phys Occup Ther Pediatr 2003; 23: 31–50.
- 40. Wright FV, Boschen K, Jutai J. Exploring the comparative responsiveness of a core set of outcome measures in a school-based conductive education programme. Child Care Health Dev 2005; 11: 156–163.
- Odman P, Oberg B. Effectiveness of intensive training for children with cerebral palsy – a comparison between child and youth rehabilitation and conductive education. J Rehab Med 2005; 37: 263–270.
- 42. Odman P, Oberg B. Effectiveness and expectations of intensive training for children with cerebral palsy – a comparison between child and youth rehabilitation and conductive education. Disabil Rehabil 2006; 28: 561–570.
- Odman P, Richt B, Oberg B. Parents' conceptions of intensive group training. The case of cerebral palsy. Disabil Rehabil 2009; 4: 293–301.
- Woolfson LH. Educational interventions for infants and preschool children with cerebral palsy: methodological difficulties and future directions in evaluation research. Eur J Special Needs Educ 1999; 14: 240–253.
- Pedersen AV. Conductive education a critical appraisal. Adv Physiother 2000; 2: 75–82.
- 46. Kanda T, Pidcock FS, Yamori Y, Shikata Y. Motor outcome differences between two groups of children with spastic diplegia who received different intensities of early onset physiotherapy followed for 5 years. Brain Dev 2004; 26: 118–126.
- Schalow G, Jaigma P. Cerebral palsy improvement achieved by coordination dynamics therapy. Electromyogr Clin Neurophysiol 2005; 47: 433–445.
- Crompton J, Imms C, Mc Coy AT, Randall M, Eldridge B, Scoullar B, et al. Group-based task-related training for children with cerebral palsy: a pilot study. Phys Occup Ther Pediatr 2007; 27: 43–65.
- Salem Y, Goodwin EM. Effects of task-oriented training on mobility function in children with cerebral palsy. Neurorehabilitation 2009; 24: 307–313.
- Löwing K, Bexelius A, Brogren-Carlberg E. Goal-directed functional therapy: a longitudinal study on gross-motor function in children with cerebral palsy. Disabil Rehabil 2010; 32: 908–916.
- Bower E, Michell D, Burnett M, Campbell MJ, McLellan DL. Randomized controlled trial of physiotherapy in 56 children with CP followed for 18 months. Dev Med Child Neurol 2001; 43: 4–15.
- 52. Löwing K, Bexelius A, Brogren CE. Activity focused and goal directed therapy for children with cerebral palsy – do goals make a difference? Disabil Rehabil 2009; 19: 1–9.
- 53. Hutzler Y, Chacham A, Bergman U, Szeinberg A. Effects of a movement and swimming program on vital capacity and water orientation skills for children with cerebral palsy. Dev Med Child Neurol 1998; 40: 176–181.
- Hutzler Y, Chacham A, Bergman U, Reches I. Effects of a movement and swimming program on water orientation skills and selfconcept of kindergarten children with cerebral palsy. Percept Mot Skills 1998; 86: 111–118.
- 55. Thorpe DE, Reilly M, Case L. The effects of an aquatic resistive exercise program on ambulatory children with cerebral palsy. J Aquat Phys Ther 2005; 13: 21–34.
- 56. Ozer D, Nalbant S, Aktop A, Duman O, Keles I. Swimming training program for children with cerebral palsy: body perceptions, problem behaviour and competence. Perc Motor Skills 2007; 105;

3:777-787.

- MacKinnon JR, Noh S, Lariviere J, MacPhail A, Allan DE, Laliberte D. A study of therapeutic effects of horseback riding for children with cerebral palsy. Phys Occup Ther Pediatr 1995; 15: 17–34.
- 58. Quint C, Toomey M. Powered saddle and pelvic mobility: an investigation into the effects on pelvic mobility of children with cerebral palsy of a powered saddle which imitates the movements of a walking horse. Physiotherapy 1998; 84: 376–384.
- 59. Mc Gibbon NH, Andrade CK, Widener G, Cintas HL. Effect of an equine-movement therapy program on gait, energy expenditure and motor function in children with spastic cerebral palsy: a pilot study. Dev Med Child Neurol 1998; 40: 754–762.
- Kuczynski M, Slonka KS. Influence of artificial saddle riding on postural stability in children with cerebral palsy. Gait Posture 1999; 10: 154–160.
- Haehl V, Giuliani C, Lewis C. Influence of hippotherapy on the kinematics and functional performance of two children with cerebral palsy. Pediatr Phys Ther 1999; 11: 89–101.
- Sterba JA, Rogers BT, France AP, Vokes DA. Horseback riding in children with cerebral palsy: effect on gross motor function. Dev Med Child Neurol 2002; 44: 301–308.
- Benda W, McGibbon NH, Grant KL. Improvements in muscle symmetry in children with cerebral palsy after equine-assisted therapy (hippotherapy). J Altern Complement Med 2003; 9: 817–825.
- 64. Cherng RJ, Liao HF, Leung HWC, Hwang AW. The effectiveness of therapeutic horseback riding in children with spastic cerebral palsy. Adapt Phys Act Quart 2004; 21: 103–121.
- Casady RL. The effect of hippotherapy on ten children with cerebral palsy. Pediatr Phys Ther 2004; 16: 165–172.
- Zurek G, Dudek K, Pirogowic I, Dziuba A, Pokorski M. Influence of mechanical hippotherapy on skin temperature responses in children with cerebral palsy. J Physiol Pharmacol 2008; 59: 819–824.

- Shurtleff TL, Standeven JW, Engsberg JR. Changes in dynamic trunk/head stability and functional reach after hippotherapy. Arch Phys Med Rehab 2009; 90: 1185–1195.
- Mc Gibbon NH, Benda W, Duncan BR. Immediate and long-term effects of hippotherapy on symmetry of adductor muscle activity and functional ability in children with spastic cerebral palsy. Arch Phys Med Rehabil 2009; 90: 966–974.
- 69. Davis E, Davies B, Wolfe R, Raadsveld R, Heine B, Thomason P, et al. A randomized controlled trial of the impact of therapeutic horse riding on the quality of life, health and function of children with cerebral palsy. Dev Med Child Neurol 2009; 51: 111–119.
- Debuse D, Gibb C, Chandler C. Effects of hippotherapy on people with cerebral palsy from the users' perspective: a qualitative study. Physiother Theory Practice 2009; 25: 174–193.
- Mac Kinnon JR, Noh S, Laliberte D, Lariviere D, Allen DE. Therapeutic horseback riding: a review of literature. Phys Occup Ther Pediatr 1995; 15: 1–15.
- Sterba JA. Does horseback riding therapy or therapist-directed hippotherapy rehabilitate children with cerebral palsy? Dev Med Child Neurol 2007; 49: 68–73.
- 73. Snider L, Korner-Britensky N, Kammann C, Warner S, Saleh M. Horseback riding as therapy for children with cerebral palsy: is there evidence of its effectiveness? Phys Occup Ther Pediatr 2007; 27: 5–23.
- 74. Darrah J, Law MC. Pollock N, Wilson B, Russell DJ, Walter SD, Rosenbaum P, Galuppi B. Context therapy: a new intervention approach for children with cerebral palsy. Dev Med Child Neurol 2011; 53: 615–620.
- 75. Law MC, Darrah J, Pollock N, Wilson B, Russell DJ, Walter SD, et al. Focus on function: a cluster, randomized controlled trial comparing child-vs context focused intervention for young children with cerebral palsy. Dev Med Child Neurol 2011; 53: 621–629.