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NEUROLOGICAL UPDATE

Neurorehabilitation: applied neuroplasticity

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Abstract The prevalence of disability due to neurological conditions is escalating worldwide. Neurological disorders have significant disability-burden with long-term functional and psychosocial issues, requiring specialized rehabilitation services for comprehensive management, especially treatments tapping into brain recovery 'neuroplastic' processes. Neurorehabilitation is interdisciplinary and cross-sectorial, requiring coordinated effort of diverse sectors, professions, patients and community to manage complex condition-related disability. This review provides evidence for a range of neurorehabilitation interventions for four common neurological conditions: multiple sclerosis (MS), stroke, traumatic brain injury and Parkinson's disease using the Grade of Recommendation, Assessment, Development and Evaluation tool for quality of evidence. Although, existing best-evidence for many interventions is still sparse, the overall findings suggest 'strong' evidence for physical therapy and psychological intervention for improved patient outcomes; and. 'moderate' evidence for multidisciplinary rehabilitation for longer term gains at the levels of activity (disability) and participation in MS and stroke population. The effect of other rehabilitation interventions is inconclusive, due to a paucity of methodologically robust studies. More research is needed to improve evidence-base for many promising rehabilitation interventions.

Keywords Neurological disorder · Rehabilitation · Neuroplasticity · Disability

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Introduction

Neurological disorders, a diverse set of conditions resulting from injury or disease of the nervous system, affect up to 1 billion people worldwide and constitute 6.3 % of the global burden of disease [1]. The disease-burden of these conditions is projected to increase by 12 % to 103 million in 2030 from an estimated 92 million disability-adjusted life-years (DALYs) in 2005 [1]. Cerebrovascular disease (stroke) contributes more than half the burden in DALYs of neurological conditions overall [1]. Neurological disorders cause nearly 12 % of total deaths globally, with cerebrovascular diseases contributing almost 85 % of these deaths [1]. The mortality rates related to neurological conditions are significantly higher in lower-middle income countries compared with high-income countries (16.8 vs. 13.2 %) [1, 2].

Although musculoskeletal conditions (such as arthritis, trauma) are prevalent and cause disability; neurological conditions have diverse symptoms, longer and more variable time course and can cause complex disabilities, including physical, cognitive, behavioural and communication deficits [3]. These conditions are costly, with socioeconomic implications due to increased demand for health care, social and vocational services, and caregiver burden [4]. Despite improved medical care and survival, people with neurological conditions have significant long-term functional and psychosocial issues that limit daily activity and participation [4]. These require integrated, interdisciplinary, collaborative care in hospital and community to enable people to live independently in the community. There are, however, major gaps in care and also important clinical areas of overlap in the collaborative and coordination efforts between services involved in the management of persons with various neurological conditions [5].

Neuroplasticity

Neuroplasticity is the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function and connections [6]. The brain is a self-organising system that adapts to its specific environment throughout pre- and post-natal life [7]. Self-organisation is defined as evolution of a system into an organized form in the absence of external pressures [8]. Understanding adaptive behaviour in response to nervous system injury requires an understanding of the interaction between the subsystems of the body, the environment, and the continuous feedback between the nervous system, the body and environment.

Since the nervous system and periphery develop together during the life of an organism, there is extensive matching between their properties, e.g. motor neurons and the muscles they innervate [9]. Injury to a part of the body can lead to changes in the nervous system. For example, limb immobilization after a tibial fracture in rats has been shown to induce exaggerated neuropeptide signalling and inflammatory changes in the spinal cord [10]. Injury to the nervous system itself, e.g. brachial plexus lesion [11], or spinal cord injury [12] leads to significant reorganization of not only the cortical representations of the affected and unaffected regions of the body, but also of spinal pathways and circuits [12]. Indeed, damage to the nervous system can lead to substantial disruption of neural networks underlying motor, sensory and cognitive functions. While brain plasticity is frequently viewed as a positive phenomenon, there may be negative consequences, such as the development of epilepsy after traumatic brain injury [13] or chronic pain after amputation or spinal cord injury [14].

Post-injury experience is a potent modulator of recovery of function. Studies in laboratory animals have shown that placing animals in complex, stimulating environments can optimise functional recovery from various forms of experimental brain damage [15]. Such environments not only afford opportunities for movement, but also expose the animals to complex perceptual and spatial stimuli. It has been hypothesized that such environments may increase the synthesis of neurotrophic factors, which in turn facilitate synaptic plasticity [16]. Beneficial effects of environmental enrichment and exercise have been shown in a wide variety of animal models of brain disorders; these include cognitive enhancement, delayed disease onset, enhanced cellular plasticity and associated molecular processes [17]. Outside of therapy sessions, patients undergoing rehabilitation spend most of their time alone and inactive [18]. Questions have been raised as to whether the rehabilitation environment is conducive to their recovery. In the area of traumatic brain injury, there is evidence that a lack of environmental enrichment may play a role in post-acute cognitive and neural decline [19].

Animal studies have shown that task-specific training and repetitive exercise are key factors in promoting synaptogenesis and are central elements in rehabilitation of motor weakness following stroke [20]. Skill acquisition and transfer of skills to other activities have been shown to be more effectively achieved with the incorporation of context-relevant task-specific meaningful activities compared to rote exercise or passive modalities [21]. Both timing and dose of therapy are important, with earlier intervention post-injury being more effective than delayed intervention, and the amount of, and opportunities to practice being critical factors [22].

Physical training in humans may be limited because constraints in certain subsystems may prevent appropriate practice of tasks. For example, spastic muscles, which may be shorter and stiffer than normal muscles [23] may be associated with contractures and subsequent biomechanical abnormalities. Weakness is one of the negative features of the Upper Motor Neuron Syndrome [24] reflected in deficiencies in generating force and in sustaining force output [25]. Addressing these issues, which result in disrupted feedback, and provision of an appropriate training environment, are highly likely to enhance functional recovery.

An understanding of the interdependence between the body and the nervous system and multiple factors contributing to motor, sensory and cognitive functions is fundamental to provision of appropriate rehabilitation for people with neurological dysfunction.

Evidence for rehabilitation interventions in common neurological conditions

Neurorehabilitation is the delivery of a coordinated interdisciplinary care program comprising ‘a set of measures that assist individuals who experience disability to achieve and maintain optimal function in interaction with their environment’ [2, 26], for maximum independence and social reintegration [1, 3]. The treating multidisciplinary team includes professionals such as neurologists, rehabilitation physicians, nurses and allied health professionals, and involve the efforts of researchers from various disciplines such as clinical medicine, neurophysiology, physiotherapy, biomechanics, and biomedical engineering [2, 27]. Overall, neurorehabilitation is a complex medical process and offers a series of therapies, which are individualized and goal-oriented to meet the specific needs of patients [28]. The framework for provision of rehabilitation is the International Classification of Functioning, Disability and Health (ICF) framework, where activity limitation (e.g. mobility, continence, self-care) and participation restriction (e.g. work, driving, community activities) interact with contextual factors (environmental, personal) that influence the performance and participatory outcomes [29].

Despite advances in medical and surgical management, neurological insults continue to cause greater disability-burden over long periods of time. In current practice, the care model for most of the neurological conditions includes both pharmacological and non-pharmacological interventions. Advances in the understanding of brain function and recovery from injury, and the development of new technologies have prompted researchers to explore new interventions, to promote functional recovery in patients with neurological disorders [30]. The body of research investigating the effect of these interventions on management of neurological conditions is growing. Newer non-invasive neuro-modulatory therapies such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), which can modulate cortical excitability, are currently being trialled in neurorehabilitation settings [30–32]. However, the therapeutic value of these new approaches is still to be established [30]. The benefit and harm associated with most neurorehabilitation interventions needs to be established to guide treating clinicians. Therefore, the following section of the review systematically evaluates existing evidence for the effectiveness and safety of rehabilitation interventions for management of four of the most common neurological conditions [stroke, multiple sclerosis (MS), traumatic brain injury (TBI) and Parkinson's disease (PD)].

Methods

A comprehensive search of the Cochrane Library database was undertaken till 12th January 2016 for systematic reviews evaluating rehabilitation interventions for four common neurological conditions: stroke, MS, TBI and PD. The search strategy included combinations of multiple search terms for two themes: neurological condition, and interventions (rehabilitation). All systematic reviews, meta-analyses of randomised controlled trials (RCTs) registered in the Cochrane Library database that evaluated rehabilitation interventions in management of the four aforementioned neurological conditions were included. Systematic reviews involving other medical conditions, where data were specifically provided for aforementioned neurological conditions, were also included. Where high quality systematic reviews or meta-analyses were identified, reviews published prior to the date of that review's search strategy were excluded. The exclusion criteria were paediatrics and reviews evaluating pharmacological or surgical intervention, or diagnostic procedures.

Study selection and data extraction

Two authors (BA, FK) independently screened and shortlisted all abstracts and titles of reviews identified by the search strategy for inclusion and appropriateness based on the selection criteria. Each study was evaluated independently by the authors, and the full text of the article obtained for further assessment to determine whether it met the inclusion/exclusion criteria. If no consensus was reached regarding the possible inclusion/exclusion of any individual study, a final consensus decision was made with other authors (JK, MG). Data extraction was conducted by two authors (BA, FK) independently, using a standard proforma. The information obtained from all included reviews included: publication and search date, objectives, characteristics of included studies and study subjects, intervention, findings/patient outcomes in the review for which data were available, and limitations. Any discrepancies were resolved by all authors re-reviewing the study. The Grade of Recommendation, Assessment, Development and Evaluation (GRADE) tool was used to assess the quality of evidence for each type of interventions [33].

Results

The search retrieved 78 published systematic reviews in the Cochrane Library database evaluating rehabilitation interventions for management of four common neurological conditions (MS, stroke, TBI, and PD). Of these, 58 reviews fulfilled the inclusion criteria for this review: MS (12 reviews), stroke (30 reviews), TBI (8 reviews) and PD (8 reviews). The rehabilitation programs evaluated included a wide spectrum of interventions. Of the included reviews, the majority ($n = 15$ reviews) evaluated different physical activity programs in isolation or concomitant with other interventions. Thirteen reviews evaluated psychological interventions.

Current evidence for the rehabilitation interventions

Neurological conditions are complex, and the activity of a person with a neurological insult can be affected by a combination of motor (weakness, spasticity), sensory (proprioception loss, ataxia), fatigue, psychological and visual impairments, and others. Improving or restoring physical and psychosocial abilities is, therefore, a key issue in rehabilitation. It requires coordinated management with interdisciplinary input from medical (neurologist, rehabilitation physician and others), nursing, allied health [physiotherapy (PT), occupational therapy (OT), social work, psychologist and others [34]. The interventions are often patient-centred, time-based, functionally oriented and aim to maximise activity and participation (social integration) with appropriate follow-up, education and support for patients (and carers) [34].

The existing best-evidence synthesis for rehabilitation interventions in the four common neurological conditions (MS, stroke, PD and TBI) are summarised in Table 1. The findings indicate that, although a broad spectrum of interventions are used in rehabilitation, the evidence for many of these is limited and/or unclear due to a paucity of robust, methodologically strong studies. The overall findings of this review suggest:

High quality evidence for:

- Physical therapy (exercise/physical activities) for improved functional outcomes (mobility, muscle strength, aerobic capacity), reduced fatigue and improved quality of life (QoL) in MS,
- Cardiorespiratory training in reducing disability after stroke.

Moderate quality evidence for:

- Multi-disciplinary rehabilitation (MDR) for long-term gains at the level of activity (disability) and participation in MS,
- Cognitive behavioural therapy (CBT) for treatment of depression, and helping people adjust to, and cope with, MS,
- Information provision in increasing patient's knowledge in MS,
- Intensive MDR for earlier functional gain in persons with moderate-severe acquired brain injury,
- Rhythmic auditory stimulation (music therapy) for improved gait parameters in stroke patients
- PT for short-term (<3-months) improvements in gait, functional mobility, balance and clinician-rated disability in PD,
- Treadmill training for improved gait speed and stride length in PD,
- CBT for acute stress disorders after mild TBI, and combination of CBT and neurorehabilitation for anxiety in mild-moderate TBI,
- Early nutritional support reveals a trend towards better outcomes in terms of survival and disability in persons with TBI.

Low quality evidence for:

- Psychological interventions for cognitive symptoms in MS,
- Telerehabilitation in reducing short-term disability and/or improving symptoms (such as fatigue, pain, insomnia), and functional activities in the longer-term; and improving QoL and psychological outcomes in MS,
- Physical therapy (such as treadmill training, circuit class therapy, repetitive task training, stretching, passive exercises and mobilization) for improved function and mobility in stroke,
- Outpatient MDR in improving active function following botulinum toxin for upper limb spasticity in chronic stroke patients
- Electromechanical and robot-assisted training in improving walking and upper limb function after stroke,
- Virtual reality and interactive video gaming in improving upper limb function and activities of daily living (ADL) in stroke patients,
- Mirror therapy as an adjunct to standard rehabilitation in improving upper extremity motor function, ADL and pain for patients after stroke,
- Cognitive rehabilitation in combination with other rehabilitation treatments in improving upper extremity function and attention after stroke,
- Exercise on reducing the impact of fatigue on ADL or fatigue severity in persons with PD,
- Whole Body Vibration (WBV) in improving gait in PD.

The evidence for other rehabilitation interventions was inconclusive, due to the limited number or lack of studies in these areas.

Discussion

The prevalence of neurological disorders is escalating worldwide adding to the economic burden for national healthcare systems. These conditions are complex and patients frequently present with, in addition to motor and sensory deficits, impaired cognitive skills, behavioural and communication issues, which require specific coordinated long-term multidisciplinary care. Recent clinical and technological advances have contributed to a better understanding of the nervous system and its response to injury, and the development of innovations such as robotics and human–machine interfaces [27]. These advances hold promise for improving care and show a great potential in neurorehabilitation, which is on the verge of a paradigm shift from traditional approaches to the use of technology [27].

Table 1 Evidence for various rehabilitation interventions in MS, stroke, TBI and PD (based on published Cochrane reviews)

Interventions	Conditions	Study, year	Number of studies, participants	Key findings	Quality of the evidence (GRADE)[a]
Multidisciplinary (MD) rehabilitation	MS	Khan et al. (updated 2011) [34]	9 RCTs and 1 CCT, 954 participants	Good evidence to support inpatient MD rehabilitation in producing short-term gains at the levels of activity (disability) and participation in patients with MS	Moderate
	ABI	Turner-Stokes et al. (updated 2015) [40]	14 RCTs and 5 CCTs, 3480 participants	Good evidence for effectiveness of intensive MD rehabilitation in earlier functional gain for person with moderate to severe ABI	Moderate
	Stroke	Aziz et al. [47]	5 RCTs, 487 participants	Inconclusive evidence as to whether therapy-based rehabilitation intervention 1 year after stroke was able to influence any relevant patient or carer outcome	Very low
		Demetrios et al. [48]	3 RCTs, 91 participants	Low level evidence for the effectiveness of outpatient MD rehabilitation in improving active function and impairments following botulinum toxin for upper limb spasticity in adults with chronic stroke	Low
Physical exercise	MS	Rietberg et al. [49]	9 RCTs, 260 participants	Strong evidence for exercise-based rehabilitation in terms of improving muscle power, exercise tolerance and mobility-related activities	High
		Heine et al. [50]	45 RCTs, 2250 participants	Strong evidence of exercise therapy on fatigue in and a larger effect was associated with endurance training, mixed training, and other training (yoga)	High
	Stroke	Saunders et al. [51]	45 trials, 2188 participants	Strong evidence suggesting cardiorespiratory training reduces disability after stroke; insufficient evidence to support the use of resistance training and unclear evidence on effects of any physical training on death and dependence after stroke	High
		States et al. [52]	9 RCTs, 499 participants	Insufficient evidence to determine if overground physical therapy gait training benefits gait function in patients with chronic stroke	Very low
		Mehrholz et al. [53]	44 trials, 2658 participants	Treadmill training with or without body weight support did not have any beneficial effects on independent walking ability, however, treadmill training with body weight support improved the walking velocity and walking endurance	Low
		Xiao et al. [54]	2 RCTs, 66 participants	Inconclusive evidence to support inspiratory muscle training as an effective treatment to improve function after stroke	Very low
		Pollock et al. [55]	13 RCTs, 603 participants	Inconclusive evidence relating to interventions in improving ability to sit-to-stand (task-specific practice of rising to stand) independently in persons with stroke	Very low
		English et al. [56]	6 RCTs, 292 participants	Circuit class therapy was found to safe and effective in improving mobility for people after moderate stroke and may reduce inpatient length of stay	Low

Table 1 continued

Interventions	Conditions	Study, year	Number of studies, participants	Key findings	Quality of the evidence (GRADE)[a]
		French et al. [57]	14 RCTs, 659 participants	Low level evidence to support the beneficial effect of repetitive task training in lower limb function, but not upper limb function	Low
		Winter et al. [58]	3 RCTs, 86 participants	Limited evidence to support the benefit of stretching, passive exercises and mobilization, when applied to the hemiplegic upper limb following stroke	Low
	TBI	Hassett et al. (edited 2009) [59]	6 RCTs, 3.0 participants	Inconclusive evidence to support the effectiveness of fitness training in improving cardio-respiratory fitness in persons with TBI	Very low
	PD	Tomlinson et al. [60]	39 RCTs, 1827 participants	PT significantly improved the gait; functional mobility and balance outcomes and clinician-rated disability for shorter-term (<3-months) compared to no intervention in persons with PD	Moderate
		Tomlinson et al. [61]	43 RCTs, 1673 participants	Inconclusive evidence to support or refute the effectiveness of one PT intervention over another in persons with PD	Very low
		Mehrholz et al. [62]	18 RCTs, 633 participants	Treadmill training improved clinically relevant gait parameters such as gait speed and stride length, in patients with PD	Moderate
		Elbers et al. [63]	2 RCTs, 57 participants	Low quality evidence for the effect of exercise on reducing the impact of fatigue on ADL or fatigue severity	Low
Mirror therapy	Stroke	Thieme et al. [64]	14 RCTs, 567 participants	Mirror therapy was favourable in improving upper extremity motor function, ADL and pain, as an adjunct to normal rehabilitation for patients after stroke	Low
Hydrotherapy	Stroke	Mehrholz et al. [65]	4 RCTs, 94 participants	Inconclusive evidence to confirm or refute water-based exercises after stroke might help to reduce disability after stroke	Very low
Electromechanical and robotic-assisted training devices	Stroke	Mehrholz et al. [66]	23 trials, 999 participants	Electromechanical-assisted gait training in combination with PT increased the odds of participants becoming independent in walking after stroke	Low
		Mehrholz et al. [67]	34 trials, 1160 participants	Low level evidence in favour of the electromechanical and robot-assisted arm and hand training after stroke in improving patients' ADL, upper limb function and muscle strength	Low
Interactive computer and video games	Stroke	Laver et al. [68]	37 RCTs, 1019 participants	Low level evidence to support the beneficial effects of virtual reality and interactive video gaming in improving upper limb function and ADLs when used as an adjunct to usual care (to increase overall therapy time) or when compared with the same dose of conventional therapy	Low
Constraint-induced movement therapy (CIMT)	Stroke	Corbetta et al. [69]	42 studies, 1453 participants	CIMT was associated with limited improvements in motor impairment and motor function, however, these benefits did not convincingly reduce disability	Low

Table 1 continued

Interventions	Conditions	Study, year	Number of studies, participants	Key findings	Quality of the evidence (GRADE)[a]
Hyperbaric oxygen therapy (HBOT)	MS	Benett and Herd [70]	9 RCTs, 504 participants	Inconclusive evidence to confirm a beneficial effect of HBOT for the treatment of MS	Very low
	TBI	Bennett et al. (updated 2009) [71]	7 RCTs, 571 participants	Good evidence for HBOT as adjunctive therapy in reduction of risk of death in TBI, but insufficient evidence that HBOT improves outcomes (QoL) in survivors	Moderate
Hyperventilation therapy	TBI	Schierhout and Roberts (updated 2009) [72]	1 RCT, 113 participants	Limited evidence for any potential benefits or harm that might result from hyperventilation therapy in improving patient outcomes in persons with TBI	Very low
Colling therapy	Stroke	Den Hertog et al. [73]	8 RCTs, 423 participants	No evidence to support routine use of physical or pharmacological strategies to reduce temperature in patients with acute stroke	Very low
	TBI	Saxsena et al. [74]	No RCTs	No evidence of modest cooling therapies (defined as any drug or physical therapy aimed at maintaining body temperature between 35 and 37.5 °C) applied to patients in the first week after TBI	NA
Whole body vibration (WBV)	MS	Sitja Rabert et al. [75]	4 RCTs, 64 participants	No evidence of a short-term or long-term effect of WBV on body balance, gait, muscle performance or quality of life	Very low
	PD	Sitja Rabert et al. [73]	6 RCTs, 236 participants	Some evidence to support single session of WBV in improvement of gait	Low
Nerve stimulation programs	Stroke	Elsner et al. [31]	15 RCTs, 455 participants	Low evidence to support the effectiveness of tDCS (anodal/cathodal/dual) for improving ADL performance and function after stroke	Low
		Elsner et al. [76]	5 RCTs, 54 participants	No evidence of the effectiveness of tDCS (anodal tDCS, cathodal tDCS) in improving aphasia in all person with stroke	Very low
		Elsner et al. [77]	12 RCTs, 136 participants	No evidence of the effectiveness of tDCS (anodal tDCS, cathodal tDCS) in improving aphasia in person with aphasia after stroke	Very low
		Hao et al. [78]	19 RCTs, 588 participants	Inconclusive evidence to support the routine use of rTMS for the treatment of stroke	Very low
	Head injury	Lombardi et al. (edited 2009) [79]	1 RCT and 2 CCTs, 68 participants	Limited evidence to support, or refute the effectiveness of multisensory programs in patients with coma and vegetative state	Very low
OT	MS	Steultjens et al. [80]	1 RCT and 2 CCTs, 274 participants	Inconclusive evidence for beneficial effects of OT in persons with MS	Very low
	Stroke	Fletcher-Smith et al. [81]	1 RCT, 118 participants	Inconclusive evidence to support or refute the efficacy of OT interventions for improving, restoring or maintaining independence in ADL for stroke survivors residing in care homes	Very low

Table 1 continued

Interventions	Conditions	Study, year	Number of studies, participants	Key findings	Quality of the evidence (GRADE)[a]
	PD	Dixon et al. [82]	2 RCTs, 84 participants	Inconclusive evidence to support or refute the efficacy of OT in persons with PD.	Very low
Speech and language therapy (SLT)	PD	Herd et al. [83]	3 RCTs, 63 participants	Inconclusive evidence to conclusively support or refute the efficacy of SLT for speech problems in PD	Very low
		Herd et al. [84]	6 RCTs, 159 participants	Inconclusive evidence to support or refute the efficacy of any form of SLT over another to treat speech problems in patients with PD	Very low
Psychological interventions	MS	Rosti-Otajärvi et al. [85]	20 RCTs, 986 participants	Low level evidence supporting neuropsychological rehabilitation in reducing cognitive symptoms in persons with MS	Low
		das Nair et al. [86]	8 RCTs, 521 participants	No evidence to support the effectiveness of memory rehabilitation on memory function or functional abilities immediately or long-term in patients with MS	Very low
		Thomas et al. [87]	16 RCTs, 1006 participants	CBT was found to be beneficial in the treatment of depression, and in helping people adjust to, and cope with, having MS	Moderate
	Stroke	Barclay-Goddard et al. [88]	6 RCTs, 119 participants	Limited evidence to suggest that mental practice in combination with other rehabilitation treatment appears to be beneficial in improving upper extremity function after stroke	Low
		Bowen et al. [89]	23 RCTs with 628 participants	Inconclusive evidence to support or refute the effectiveness of cognitive rehabilitation intervention for reducing the disabling effects of neglect and increasing independence in persons with stroke	Very low
		Cheng et al. [90]	1 RCT, 411 participants	Inconclusive evidence to support the use of motivational interviewing for improving ADL after stroke	Very low
		Loetscher et al. [91]	6 RCTs, 223 participants	Limited evidence to support cognitive rehabilitation in improving some aspects of attention in the short term, but insufficient evidence to support or refute the persisting effects of cognitive rehabilitation on attention, or on functional outcomes	Low
		Nair et al. [92]	2 RCTs, 18 participants	No evidence to support or refute the effectiveness of memory rehabilitation on functional outcomes, and objective, subjective, and observer-rated memory measures	Very low
	Stroke, ABI	Chung et al. 2013 [93]	19 RCTs, 907 participants	Inconclusive evidence for the effectiveness of cognitive rehabilitation on executive function in persons with ABI	Very low
	TBI	Lane-Brown and Tate [94]	1 RCT, 21 participants	No evidence for use of interventions for apathy such as cranial electrotherapy stimulation in persons with TBI	Very low
		Soo and Tate (updated 2009) [95]	2 RCTs, 44 participants	Good evidence for effectiveness of CBT for treatment of acute stress disorder following mild TBI; and combination of CBT and neurorehabilitation for treatment of general anxiety symptoms for mild to moderate TBI	Moderate

Table 1 continued

Interventions	Conditions	Study, year	Number of studies, participants	Key findings	Quality of the evidence (GRADE)[a]
Nutritional support	MS	Farinotti et al. [96]	6 RCTs, 794 participants	Dietary intervention including polyunsaturated fatty acids (PUFAs) (omega-6 fatty acids, linoleic acid and omega-3 fatty acids) did not have a significant effects on the clinical outcomes in MS (disease progression)	Low
		Jagannath et al. [97]	1 RCT, 49 participants	Some evidence of the potential benefit of the escalating doses of vitamin D intervention on relapse rate; disability scores; suppression of T cell proliferation	Low
	Head injury	Perel et al. (updated 2008) [98]	11 RCTs, 534 participants	Good evidence that early nutritional support associated with fewer infections and a trend towards better outcomes in terms of survival and disability	Moderate
Music therapy	ABI	Bradt et al. [99]	7 RCTs, 184 participants	Good evidence that rhythmic auditory stimulation may be beneficial for improving gait parameters, particularly in stroke patients	Moderate
Vocational rehabilitation	MS	Khan et al. [100]	1RCT and 1 CCT, 80 participants	Inconclusive evidence to support outcomes of vocational programs in the MS population.	Very low
	ABI	George et al. [101]	4 RCTs, 245 participants	Inconclusive evidence to reach conclusions about the use of rehabilitation to improve on-road driving skills after stroke	Very low
Telerehabilitation	MS	Khan et al. [102]	9 RCTs, 531 participants	Low level evidence for the effectiveness of telerehabilitation in reducing short-term disability and/or improving symptoms and impairments (such as fatigue, pain, insomnia); in improving functional activities in the longer-term; and improving QoL and psychological outcomes	Low
	Stroke	Laver et al. [103]	10 RCTs, 933 participants	Inconclusive evidence to reach conclusions about the effectiveness of telerehabilitation after stroke and to determine which intervention approaches were most appropriately adapted to a telerehabilitation approach	Very low

High quality Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality We are very uncertain about the estimate

ABI acquired brain injury, *ADL* activities of daily living, *CBT* cognitive behavioural therapy, *CCT* clinical controlled trial, *HBOT* hyperbaric oxygen therapy, *MS* multiple sclerosis, *OT* occupational therapy, *PD* Parkinson's disease, *PT* physical therapy, *QoL* quality of life, *RCT* randomised controlled trial, *SLT* speech and language therapy, *TBI* traumatic brain injury, *tDCS* transcranial direct current stimulation, *WBV* whole body vibration

[a] GRADE Grade of Recommendation, Assessment, Development and Evaluation Working Group grades of evidence

This review provides an evidence-based overview of the effectiveness of rehabilitation interventions for persons with four common neurological conditions; MS, stroke, TBI and PD. Despite an intensive search of the Cochrane Library database, most reviews evaluating rehabilitation interventions were predominantly in persons with stroke and the most common interventions evaluated were different forms of physical therapy, followed by psychological interventions. The existing best-evidence synthesis for many of the rehabilitation interventions in persons with these four neurological conditions is still sparse. The overall findings suggest 'strong' evidence for physical therapy and psychological interventions for improved patient outcomes in persons with MS and stroke, and 'moderate' evidence in favour of MDR in producing longer term gains at the levels of activity (disability) and participation in persons with MS and stroke. There is a 'low' quality evidence for the majority of interventions such as telerehabilitation, electromechanical and robot-assisted training, virtual reality and interactive video gaming, mirror therapy, WBV and 'inconclusive' evidence for other rehabilitation interventions due to the limited number of robust, methodologically strong studies.

Rehabilitation is a complex intervention, defined as 'complex' where the active ingredient in the intervention is not easily identifiable [35]. There are many challenges in evaluating rehabilitation interventions in neurological conditions. The evidence synthesis highlights the need for systematic data collection in the course of real-life clinical practice, as well as long-term follow-up of outcomes, by inclusion of research evidence beyond the restrictive experimental trials [randomised controlled trials (RCTs) and controlled clinical trials (CCTs)], which are the core requirements for the Cochrane reviews. Various authors have argued that though RCTs are considered the 'gold standard' for high level evidence of the effectiveness of an intervention, they might be less appropriate in studying 'complex' interventions such as rehabilitation, due to various issues, such as ethical considerations (withholding and/or delaying interventions or providing placebo); heterogeneous populations (diverse clinical presentations with varying levels of disability), interdependent components and contexts, and multifaceted, multilayered treatments involving organisational restructure, and individualised interventions [34, 36–38].

There is general consensus amongst clinical researchers about the difficulty in selection of meaningful and responsive outcome measurement tools that reflect functional gains and recovery in patients after neurological insults. The outcome measures used in the neurological population need to reflect its complex constructs and focus on impairments, activity and restriction in participation, as advocated by WHO ICF [29]. Assimilation of data from different trials poses challenges because of the marked heterogeneity in outcome measures used, assessment time points and duration of follow-up. Many of the outcomes measures used in trials were not primarily designed for specific neurological conditions, and these scales may not be sufficiently sensitive to capture the relevant gains following intervention due to the fluctuating nature of conditions such as MS, stroke [34, 39, 40]. Floor/ceiling effects of some measures (e.g. the Functional Independence Measure) may limit sensitivity to treatment effects, and even the standardised measures may behave differently in different cultures and settings [41]. Further, as persons with neurological conditions can show marked clinical heterogeneity, clinicians may not always agree with one another or incorporate the patient/carer perspective into decision making, and many issues important to patients may be missed [34, 42]. More research is needed to gain consensus on a suitable battery of measures to capture change in physical ability (at the level of impairment and disability), as well as the long-term outcomes relating to psychosocial adjustment and QoL.

An important concept in rehabilitation is learning and resilience (a process of an individuals' interaction with the environment to adapt, promote well-being or protect against the influence of risk factors) [43], which corresponds with the ICF personal and contextual factors categories. These processes may include individual coping strategies, family support, therapists, schools, communities, etc. Resilient people are those with optimistic attitudes and positive emotionality, and through practice have developed coping techniques, to effectively balance negative emotions with positive ones. Identifying factors that influence a person's resilience is vital in rehabilitation settings, which may include: ability to make realistic plans, positive self-concept and confidence, communication and problem-solving skills, ability to manage strong impulses and feelings, care and support, positive self-image. CBT has been shown to be effective in reducing depressive symptoms and in helping people adjust to MS. Further investigations of this or other interventions that can improve flexibility in thinking, problem-solving, and adaptive coping strategies are needed.

Advances in knowledge of neuroplasticity and developments in technology provide a basis for alternative efficient and cost-effective methods to deliver therapy using web-based devices (computer, mobile phones, etc.) in settings convenient for patients. In-home telerehabilitation can minimise the barriers of distance, time, cost and healthcare system load [28]. Other initiatives include use of gaming technology (computer games and upper limb robotics) [44], and provision of enriched environments to tap into neuroplastic processes as discussed [45]. Other technology, such as wearable motion sensors, allow objective assessment of motor behavior (such as physical activity and arm use.) in the community setting which reflects function in real life [46]. Such devices may eventually replace the current insensitive clinical measurement tools.

Study limitations

There are limitations regarding the completeness of retrieved literature and interpretation of the findings in this review. First, a comprehensive search was conducted only in a single Cochrane Database to capture the widest possible selection of relevant literature. The aim was to capture the most high quality reviews of RCTs. Due to the standardisation of the Cochrane reviews, we were able to critically appraise the methodological quality of all reviews, and used validated tools to assess the quality of evidence (GRADE). As we included four reviews from our own research group published in the Cochrane library, the assessment of the quality of these reviews was not independent. However, since the Cochrane Collaboration sets the standard for research synthesis, the quality of evidence appraisals of these reviews are consistent with the other included reviews, and therefore valid. Adverse events reporting was often incomplete and/or inconsistent and associated economic benefit of interventions were not reported in any reviews. However, it was beyond the scope of this review to search for evidence on the safety and economic benefits of included interventions.

Conclusion

In conclusion, neurological conditions are complex and require specialized services for comprehensive management. Therapeutic interventions need to tap into brain recovery processes and include enriched environments. This review found limited but promising evidence to support the effectiveness of different rehabilitation interventions in reducing disability and enhancing participatory outcomes in persons with common neurological diseases. More research is needed to improve the evidence-base for many promising rehabilitation interventions. Future research should focus on interventions that can be integrated into a MDR program and engage, educate, and empower patients.

Compliance with ethical standards

Conflicts of interest The authors declare no conflicts of interest.

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