Université catholique de Louvain

Secteur des sciences de la santé - Sciences de la motricité

Institut de recherche expérimentale et clinique - IREC

Institute of Neuroscience (IoNS)

The use of robotics and serious games in neurorehabilitation: from general principles to clinical validation and practice

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Thesis submitted in fulfilment of the requirements for the degree of

“Docteur en Sciences de la Motricité”

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December 2025

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Remerciements

Je tiens tout d’abord à exprimer ma plus profonde gratitude au Professeur Thierry Lejeune, promoteur de cette thèse. Son accompagnement exemplaire, à la fois constant et empreint de justesse, a constitué un véritable modèle. Promoteur idéal, il a su allier rigueur scientifique, écoute attentive et bienveillance humaine, tout en préservant la distance nécessaire pour favoriser mon autonomie. Son exigence, sa compétence et son humanité ont été des sources d’inspiration tout au long de ce parcours.

Je remercie également le Professeur Yves Vandermeeren, copromoteur de ce travail, pour avoir accepté de m’accompagner avec bienveillance et pour la qualité de ses échanges et de ses conseils, toujours pertinents malgré la distance.

Ma reconnaissance s’adresse ensuite aux membres du jury de thèse. Le Professeur Robert Hardwick, président du comité, a assuré avec efficacité et bienveillance le suivi et l’organisation pratique des réunions. Sa réactivité, sa flexibilité et son professionnalisme ont grandement facilité le déroulement de ce projet. Le Professeur Gaëtan Stoquart, expert en réadaptation neurologique, m’a offert des critiques constructives, ainsi qu’une confiance précieuse qui m’a encouragé à progresser. J’adresse également mes sincères remerciements à la Professeure Eva Swinnen et au Docteur Franco Molteni, membres externes, pour l’intérêt qu’ils ont porté à mes travaux, leurs suggestions enrichissantes et la qualité de leurs propres recherches, qui ont constitué une véritable source d’inspiration.

Je souhaite également remercier le Professeur Martin Edwards pour son accompagnement stimulant, ses idées novatrices, sa pensée toujours “out of the box” et son humour britannique, qui ont nourri ce travail de manière singulière.

Je remercie les fonds de recherche — la Fondation Horlait-Dapsens, le Fonds Spécial de Recherche (FSR) et le Fonds National de la Recherche Scientifique (FNRS) — dont le soutien financier a rendu ce projet possible.

Ma profonde gratitude va également à tous les patients qui ont accepté de participer à ces recherches, offrant généreusement leur temps et leur énergie. Ils représentent une source perpétuelle de motivation, nourrissent et inspirent mon travail, et demeurent les récepteurs ultimes de ses résultats, car c'est avant tout pour eux que ces efforts ont été réalisés.

Je remercie l'ensemble du service de Médecine Physique et Réadaptation des Cliniques universitaires Saint-Luc. Un merci particulier à mes collègues Clara Selves, Gonzalo Rodriguez Tapia, Virginie Fraselle et Mathilde Massardier pour leur aide constante, leur disponibilité, leur précieuse amitié et leurs conseils avisés. Travailler ensemble au sein d'un hôpital universitaire permet à chacun de contribuer à la création d'une force commune qui stimule notre engagement, nous motive mutuellement et améliore la qualité des soins dispensés à nos patients. Mes remerciements vont également aux collègues du CHU Mont-Godinne, et plus spécialement à Caroline Meyer et Alexis Lheureux pour leur écoute et leur soutien, ainsi qu'aux autres collègues, Maxime Valet et Mubine Rahamatali, pour leur amitié, leur soutien et leur bonne humeur.

Je souhaite exprimer ma reconnaissance au laboratoire NMSK, et en particulier à Stéphanie Dehem, pour son accompagnement, sa patience, ses nombreuses discussions et son énergie inspirante. Merci à Gauthier Everard pour sa motivation constante, son efficacité remarquable et son enthousiasme communicatif, ainsi qu'à Virginie Otlet pour son aide toujours précieuse. Je tiens également à remercier Bruno Dehez, Alexandre Luc, Khawla Ajana et Jean-Gabriel Previnaire pour leur contribution à la rédaction des articles qui constituent ma thèse.

Je remercie le Professeur Christine Detrembleur, première à m'avoir accueilli au sein du laboratoire, pour ses conseils avisés — notamment en statistique — et pour son humanité. Merci également au Professeur Henri Nielens, qui m'a transmis le goût de la recherche dès le début de ma formation clinique, et à la Professeure Anne Berquin, pour sa présence rassurante et son soutien académique indéfectible.

Enfin, je souhaite exprimer toute ma gratitude à mes parents, Maria et Georgios, et mes proches, pour leur soutien inébranlable, leur patience et leur compréhension face aux contraintes de ces années intenses. Que ce soit en Belgique ou en Grèce, leur amour, leur intérêt et leur soutien m'a été précieux à chaque étape. Je tiens à remercier chaleureusement mon frère, Stavros, médecin aux États-Unis, pour sa présence et ses encouragements malgré la distance. Je suis profondément fier de son parcours exemplaire, qui inspire à viser l'excellence. Nos nombreux échanges sur les différences de pratiques et de systèmes de soins, ainsi que ses commentaires toujours précis et son regard pertinent, ont grandement enrichi ma réflexion et nourri mon travail.

Je souhaite aussi rendre hommage à ma famille, qui a été une source constante d'inspiration tout au long de ma thèse. Du côté des montagnes de l'Épire, je remercie ma grand-mère Afroditi, exemple de résilience et de courage, ainsi que mes tantes et oncles maternels. Du côté paternel, sous l'air inspirant de la mer Égée, je rends hommage à mes grands-parents, Ioannis et Eleftheria, décédés durant ma thèse, dont la mémoire continue de guider mes pas et d'inspirer mon engagement et mon optimisme. Je tiens également à remercier mes tantes bien-aimées, Anna-Maria et Katerina, dont l'affection et les conseils ont nourri ma confiance en moi, orientée vers l'humain, soutenu ma persévérance dans la quête de ce qui est juste, et renforcé ma volonté d'excellence au service des autres.

Et, plus que tout, à Andromachi, mon épouse, dont la présence a rendu la réalisation de tout ce travail possible. En cette année 2025 si particulière, elle m'a rempli de joie et d'espoir en m'offrant le plus beau des cadeaux : notre fille Maria-Zacharoula. Sa tendresse dans les moments difficiles, ses encouragements dans les périodes de doute et son sourire dans les instants d'épuisement ont illuminé ce parcours. Alors que nous regardons vers l'avenir, je me réjouis de poursuivre notre évolution commune, de partager encore de nombreux moments précieux et de vivre ensemble les joies et les défis des années à venir.

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Summary

Intensive rehabilitation, including exercises with individualized difficulty, is recommended to promote motor recovery after stroke or spinal cord injury. This thesis explores how robotics and serious games can support the implementation of a consolidated set of neurorehabilitation principles. We clinically validated an adaptation algorithm that adjusts in real time exercise difficulty within a serious game implemented on a distal-effector robot, combining cognitive and upper-limb motor rehabilitation after stroke. Two meta-analyses and one systematic review synthesized evidence on the effectiveness of serious games and self-rehabilitation after stroke, as well as on the use of self-balancing exoskeletons for gait training in individuals with high tetraplegia. The integration of these technologies, complementing conventional therapies, constitute an effective strategy in neurorehabilitation.

Key terms: neurorehabilitation, stroke, spinal cord injury, cognitive rehabilitation, robot-assisted therapy, motor learning, serious games.

Résumé

Une rééducation intensive, comprenant des exercices à difficulté individualisée, est recommandée pour favoriser la récupération motrice après un accident vasculaire cérébral (AVC) ou une lésion médullaire. Cette thèse explore comment la robotique et les jeux sérieux facilitent l'implémentation d'un ensemble de principes de neuroréadaptation récemment décrits dans la littérature. Nous avons validé cliniquement un algorithme ajustant de façon dynamique le niveau de difficulté d'un jeu sérieux implémenté sur un robot à effecteur distal, combinant rééducation cognitive et motrice. Deux méta-analyses et une revue systématique ont ensuite synthétisé les preuves sur l'efficacité des jeux sérieux et de l'auto-rééducation post-AVC, ainsi que sur l'usage des exosquelettes auto-balancés pour la marche chez les tétraplégiques hauts. Ces technologies, en complément des thérapies conventionnelles, constitue des stratégies à utiliser pour stimuler la récupération en neuroréadaptation.

Mots-clés : neuroréadaptation, accident vasculaire cérébral (AVC), blessé médullaire, rééducation cognitive, thérapie assistée par robot, apprentissage moteur, jeux sérieux.

Chapter I – General introduction

1.1 Context

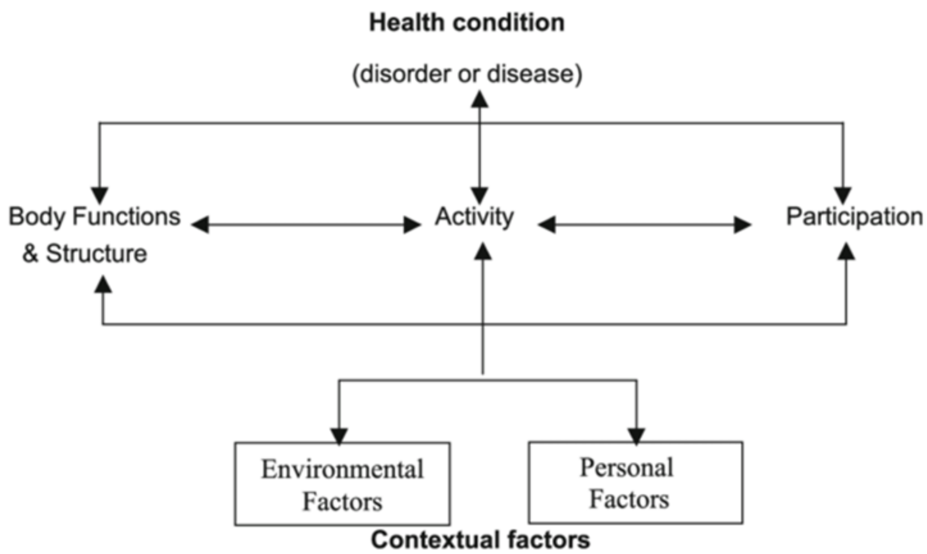
Neurological disorders, such as stroke and spinal cord injury (SCI), constitute significant health conditions and leading causes of adult disability in the world [1]. According to the World Health Organization (WHO), each year approximately 15 million people suffer from stroke and between 250.000 and 500.000 people are affected by SCI [2, 3]. Among them, more than 80% of survivors have persistent rehabilitation needs one year after stroke or SCI and more than 50% among them maintain some form of chronic disability [2, 3]. Over the past years, stroke incident has been increasing, mean age of stroke occurrence has been decreasing and success rates of revascularization therapies and mechanical thrombectomy has been increased leading to an increased number of working age adults requiring rehabilitation [2, 4]. Similarly, SCI impacts working age adults, requiring laborious medical treatments and intensive rehabilitation on the long term [3]. These trends lead to growing individual and economic burden on healthcare systems, especially regarding rehabilitation needs following acute medical care [5].

The Stroke Council of the American Heart Association/American Stroke Association characterizes stroke as a "neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intracerebral haemorrhage and subarachnoid haemorrhage" [6]. SCI refers to damage to the spinal cord and is, in most cases, caused by trauma resulting from road accidents, sports accidents, falls or acts of violence [3]. Both conditions can lead to motor and sensory impairments affecting either one side of the body (e.g. hemiplegia or hemiparesis commonly encountered after stroke) or the lower and/or upper limbs (e.g. quadriplegia or paraplegia commonly encountered after SCI).

Additionally, stroke can impact cognitive functions and/or emotional function.

The International Classification of Functioning, Disability and Health (ICF) framework (schematized in Figure 1) is used to facilitate and standardize description and organisation of information regarding the way impairments affect functioning and lead to disability [7]. This framework, approved for use by all WHO member states in 2001, provides a conceptual basis for the definition and measurement of health and disability. Additionally, according to a holistic approach, it allows an in-depth understanding of how an individual functions in everyday life and of how functioning may interact with contextual factors.

Figure 1. International Classification of Functioning, Disability and Health (ICF) framework [5].



The type and severity of impairments following a stroke vary widely based on the affected area of the brain and the extent of tissue damage. For example, common motor impairments include weakness, spasticity, poor coordination and loss of fine motor skills (especially in the hands). Common cognitive impairments include attentional deficits, executive function, memory loss and aphasia. It is estimated that, after stroke, more than two-thirds of survivors present upper limb (UL) paresis and more than one-third present with attentional deficits [8, 9]. Each combination of impairments, in terms of type and severity, can impact independence in activities of daily life (ADL) and limit social participation in various ways. In consequence, diverse profiles emerge in terms of rehabilitation needs and prognosis. Similarly, SCI can lead to various types of patients' profiles in terms of motor, sensory and autonomic nervous system deficits, usually categorized using the ASIA scale [10].

In clinical practice and research, type and severity of impairments, limitation in activities and participation restriction are evaluated using specific rating scales. A multitude of rating scales exist in scientific literature for evaluation of various types of symptoms and impairments after stroke and SCI [11]. Standardisation efforts has led to the creation of specific evaluation core sets for major health conditions, such as stroke and SCI, including specific time points at which the measurements should be performed [12]. Figure 2 and Figure 3 respectively illustrate the Brief ICF core set for stroke and SCI, indicating the included categories of each domain (Body functions, Body structures, Activities and participation, Environmental factors) for which an evaluation should be performed.

Figure 2. International Classification of Functioning, Disability and Health (ICF) – categories included in the Brief ICF Core Set for stroke and percentage of experts willing to include the named category in the Brief ICF Core Set. 50% represent a preliminary cut-off. 50% is bold [12].

ICF component	%	ICF code	ICF category title
Body functions	**100**	**b110**	**Consciousness functions**
	86	**b114**	**Orientation functions**
	82	**b730**	**Muscle power functions**
	75	**b167**	**Mental functions of language**
	50	b140	Attention functions
	25	b144	Memory functions
Body structures	**100**	**s110**	**Structure of brain**
	7	s730	Structure of upper extremity
Activities and participation	**100**	**d450**	**Walking**
	100	**d330**	**Speaking**
	93	**d530**	**Toileting**
	68	**d550**	**Eating**
	50	d510	Washing oneself
	43	d540	Dressing
	4	d310	Communicating with – receiving – spoken messages
Environmental factors	**93**	**e310**	**Immediate family**
	43	e355	Health professionals
	29	e580	Health services, systems and policies

Figure 3. International Classification of Functioning, Disability and Health (ICF) – categories included in the Brief ICF Core Set for SCI [13].

ICF component	*Rank*	*ICF code*	*Title*
Body functions	1	b730	Muscle power functions
	2	b620	Urination functions
	3	b280	Sensation of pain
	4	b525	Defecation functions
	5	b640	Sexual functions
	6	b810	Protective functions of the skin
	7	b735	Muscle tone functions
	8	b710	Mobility of joint functions
	9	b152	Emotional functions
Body structures	1	s120	Spinal cord and related structures
	2	s610	Structure of urinary system
	3	s810	Structure of areas of skin
	4	s430	Structure of respiratory system
Activities and participation	1	d530	Toileting
	2	d420	Transferring oneself
	3	d230	Carrying out daily routine
	4	d465	Moving around using equipment
	5	d410	Changing basic body position
	6	d445	Hand and arm use
	7	d470	Using transportation
	8	d455	Moving around
	9	d520	Caring for body parts
	10	d550	Eating
	11	d240	Handling stress and other psychological demands
Environmental factors	1	e310	Immediate family
	2	e120	Products and technology for personal indoor and outdoor mobility and transportation
	3	e115	Products and technology for personal use in daily living
	4	e150	Design, construction and building products and technology of buildings for public use
	5	e155	Design, construction and building products and technology of buildings for private use
	6	e110	Products or substances for personal consumption
	7	e355	Health professionals
	8	e340	Personal care providers and personal assistants
	9	e580	Health services, systems and policies

Regarding clinical motor rehabilitation after stroke, Figure 4a represents a core set of outcome measurement scales commonly used in clinical practice and research and Figure 4b indicates the specific time points at which these evaluations should be performed [14]. However, there is a lack of universal consensus regarding the specific rating scales that should be used to perform evaluations in other ICF categories, such as attentional functions.

Figure 4a. Core set of outcome measures for clinical motor rehabilitation after stroke [14].

	Body functions	Activities	Participation
Upper extremity	FMA	ARAT	SIS
Lower extremity	FMA & 10MWT*	TUG* & BBS	SIS
ADL/ stroke-specific	NIHSS	BI/ FIM	SIS

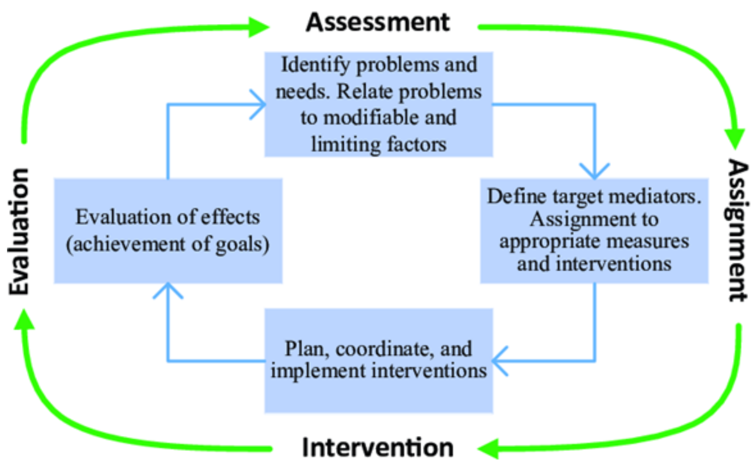
Figure 4b. Measurement time points of the core set for clinical motor rehabilitation after stroke [14].

	d 2±1	d 7	wk 2	wk 4	wk 12	wk 26	+26 wks
Body functions	✓ (1)	✓ (1)	✓	✓	✓	✓	✓
Activities		✓ (2)	✓	✓	✓ (2)	✓	✓ (2)
Participation					✓		✓

✓, recommended time point for assessment; d, day; m, month; wk, week; (1) exceptional time points for the National Institutes of Health Stroke Scale, only indicated at these time points; (2) exceptional time points for the Barthel Index/Functional Independence Measure, only indicated at these time points.

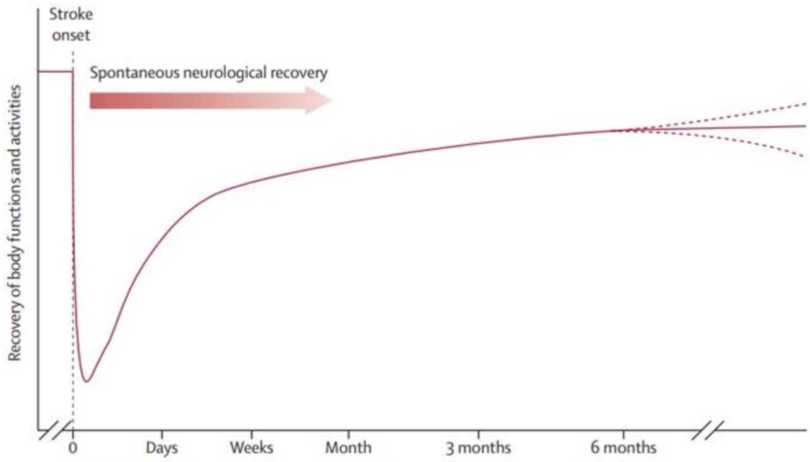
Assessment using rating scales is important, as shown in The Rehabilitation Cycle illustrated in Figure 5 [15]. First, as mentioned above, it allows identification of individual problems (impairments and limitations) and evaluation of rehabilitation needs which leads to the establishment of a personalized rehabilitation plan. Secondly, it allows follow-up using objective measures which guides goal setting and enables evaluation of effects of interventions. Finally, it promotes implementation of interventions which are most effective in specific subpopulations.

Figure 5. The Cycle of Rehabilitation [15].



Recovery profiles can vary widely after stroke in terms of degree of functional recovery [16]. Figure 6 illustrates a hypothetical pattern of recovery after stroke, according to Langhorne et al. [17]. As displayed on this graph, neurological recovery occurs mainly during the first three months following stroke. Recent findings suggest that the results of specific outcome measures, performed in early stages after stroke, have prognostic value, allowing determination of recovery potential [18].

Figure 6. Hypothetical pattern of recovery after stroke [17].



Similarly, functional recovery varies among individuals following SCI injury and is influenced by several mechanisms dictating spinal plasticity [19]. Depending on the chronicity following the injury, different pathophysiological mechanisms have been described [20]. Consequently, adequate selection of therapeutic modalities, often consisting of combinatory strategies including rehabilitation, is important in order to achieve greater functional recovery.

In order to enhance functional recovery, recent guidelines recommend intensive rehabilitation using challenging and individualized tasks [21, 22]. In clinical practice, rehabilitation is commonly performed using therapist-led interventions, usually designated in research as “conventional rehabilitation methods”, which for motor rehabilitation include physiotherapist-led gait training, occupational therapist led hand function training and ADL training. Novel, technology-based rehabilitation approaches, including robotics and serious games training, complement conventional methods by alleviating therapists’ burden through automation and by facilitating data-driven decision making.

1.2 Definition and use of robotic devices in rehabilitation of neurological disorders

Over the past decades, the use of robotic devices in neurorehabilitation, notably after stroke or SCI, has exponentially increased. Rehabilitation robots are defined as “controllable electromechanical devices designed for human interaction during rehabilitation exercises” [23].

In the context of neurological disorders, robotic devices are principally used for motor rehabilitation and more specifically for gait training and rehabilitation of the UL. This can be explained by the multiple advantages that robot assisted training (RAT) presents in this context. First, RAT allows a higher number of controlled movement repetitions when compared to conventional therapy with the same duration of therapy sessions [24]. Therapists’ time is consequently liberated and treatment of patients, especially the most severely impaired ones, becomes less strenuous. Second, therapy dosage and task-difficulty can be modulated through RAT by executing task-oriented exercises, using variable movement patterns and changing intensity by adapting assistance or resistance of the robotic device [25]. The sequence of performed movements and task-difficulty can be predetermined or adjusted in real time, based on objective measures performed through the robotic device. Third, data acquired through the device can facilitate tracking of motor recovery over time and can be used to provide feedback during and after each session [26]. Additionally, beyond training, robotic devices can be used for evaluation purposes through specific and validated modules or tasks, complementing commonly used clinical rating scales [27]. Finally, depending on the robotic device characteristics, multisensory stimulation (visual, auditory, haptic) can be incorporated to motor exercises, also contributing to real time feedback during training [28].

Robotic devices used in the context of neurorehabilitation are commonly classified in two main categories: end effector type robots and exoskeletons

[29]. On one hand, end effector type robots allow interaction with the environment through the most distal part of the robot usually with a handle for the user to grasp. Figure 7 illustrates two devices frequently used in research and clinical settings. The MIT Manus represented in Figure 7a was the first rehabilitation robot developed in the early 1990s designed for UL motor rehabilitation [30]. The REAplan®, represented in Figure 7b, is the rehabilitation robot used in this PhD thesis [31]. As illustrated in Figure 7a, the end effector is the only contact point between the user and the robot. During therapy, straps are usually used to stabilize the patient and limit occurrence of compensatory movements.

Figure 7a. MIT Manus (Massachusetts Institute of Technology) [30].

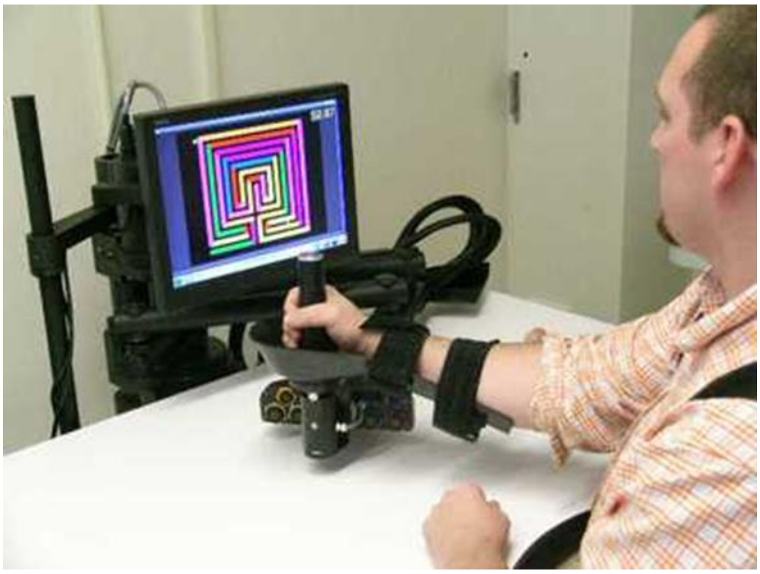


Figure 7b. REAplan® robotic device (Axinesis) [31].

On the other hand, mainly used for robot-assisted gait training (RAGT), exoskeletons are defined as “devices with anatomically-inspired form factors that mimic the structure and movement of human limbs, usually mounted on or around the limb like a brace” [23]. Exoskeletons can also be used for UL rehabilitation offering the advantage of controlling and measuring movements at each joint [29]. Figure 8 illustrates three exoskeletons: one exoskeleton used for UL rehabilitation (Figure 8a) and types of exoskeletons used for gait rehabilitation (Figure 8b&c) [32, 33, 34].

Figure 8a. ArmeoPower (Hocoma AG) [32].

It should be noted that different types of exoskeletons can be used for gait rehabilitation after stroke or SCI. One category consists of static treadmill exoskeletons, with integrated body weight support systems (BWSS), such as the Lokomat illustrated in Figure 8b [33]. A second category includes wearable powered exoskeletons (WPE) used for overground gait training, with or without UL assistance and with or without ability of self-balancing during treatment [34]. Recent developments and new specificities of certain subcategories of exoskeletons, such as self-balancing WPE, have led to the expansion of the use of these robotic devices beyond rehabilitation purposes, including their usage as support or compensation systems during activities of daily living. For example, the Atalante exoskeleton, presented in Figure 8c, is a WPE with the ability to self-balance during overground gait training [34].

Figure 8b. Lokomat (Hocoma AG) [33].

Figure 8c. Atalante exoskeleton (Wandercraft) [34].

Although the utilization of robotic devices in neurorehabilitation expands over more than thirty years, many questions regarding their efficacy and optimal usage remain unanswered to this day. After initial safety concerns linked to intensification of treatments were waived, RAT quickly became a globally accepted therapeutic modality for gait-training after SCI and then for post-stroke rehabilitation [35]. In parallel, technological improvements concerning some specificities of new prototype models, such as the above-mentioned Atalante exoskeleton, explain why some concerns remain in specific subpopulations, as for example tetraplegic patients after SCI. Consequently, potential applications of RAT in neurorehabilitation are still expanding.

A series of systematic reviews with meta-analysis have been conducted to assess efficacy of robotic devices in UL motor rehabilitation after stroke [36, 37, 38, 39]. Although evidence suggest that robotic training significantly improves motor function when compared to conventional therapist-led interventions, some controversy remains [40]. Indeed, Norouzi-Gheidari et al. suggested that when the duration/intensity of conventional therapy is dose-matched to RAT, effect sizes of both treatments are similar concerning motor control, strength and activities of daily living [37]. Another study demonstrated that although RAT leads to small yet significant improvements in motor control and muscle strength when compared to nonrobotic treatments, findings concerning activity limitation showed no differences in improvements between the two types of treatments [38]. In another meta-analysis, Zhang et al. indicated that improvements in UL function were better when RAT was used in addition to conventional treatments compared to conventional therapy alone [39]. Finally, the RATULS study, a large multicentre randomised controlled trial including 770 participants with moderate or severe UL functional limitation, didn't demonstrate significant differences in improvements concerning UL function between RAT, enhanced UL therapy and usual care [41].

Nowadays, RAT is a recommended treatment modality to be included in rehabilitation plans designed to improve UL recovery after stroke [21]. To overcome the observed differences in outcomes concerning efficacy of RAT in UL rehabilitation after stroke, scientific focus has progressively shifted towards elucidating how to more effectively employ robotics in this context. This has led to explore possibilities in different directions. First, one of the explored ways to enhance efficacy of RAT in stroke rehabilitation concerns the use of robotic devices in combination with other technologies, such as virtual reality or serious games [42]. Potential advantages and challenges related to this approach are developed in section 1.3. Importantly, combining other technologies to robotic devices opens perspectives concerning control strategies of task difficulty adaptation mechanisms utilized in RAT [43]. Combining new technologies also facilitates application of a personalized approach through objectively quantified individualized data [44]. Second, the use of robotic devices has recently been expanded to include rehabilitation of other impairments, such as cognitive deficits, typically in combination with motor rehabilitation [45]. This point is elaborated in section 1.4. Finally, these technologies offer possibilities in terms of self- and tele-rehabilitation which also constitutes an area worth investigating with the aim of strengthening current rehabilitation practices.

Robotic devices can also be used for lower limb training and gait rehabilitation after stroke and SCI [22, 46]. Concerning gait rehabilitation after SCI, recent guidelines recommend that RAGT should be included in the rehabilitation plan when possible [47]. Indeed, it has been proposed that robotic rehabilitation facilitate proprioceptive input to the spinal cord through walking-related rhythmic movements and potentially induces neuroplastic changes at the spinal cord level and the sensorimotor cortex and cerebellar regions of the brain [48]. Although efficacy of RAGT after spinal cord injury is not clearly established, a recent meta-analysis suggests better improvements in ADL, muscular strength and walking ability when compared to conventional rehabilitation [49]. Additionally, it appears that efficacy of RAGT in this context may be influenced by the choice of the robotic device (end-effector type vs exoskeleton) and the type of gait training protocol (over ground walking vs treadmill walking) [49]. More specifically, previous studies suggested that end effector type robots show better results in postural control and that exoskeletons lead to better improvements in walking speed when compared to conventional physical therapist-led interventions [49].

1.3 Definition(s) and use of serious games in neurorehabilitation

Rehabilitation after stroke and SCI in most cases consists of a lengthy process requiring high volumes of purposeful daily movement repetitions [17]. During rehabilitation, many patients are challenged by the monotony of exercises which leads to a lack of motivation and engagement issues during therapy [50]. Also, many patients experience post stroke fatigue, and some are affected by depression, which may render additional difficulties in terms of therapy consistency and may impact participation during treatments [51]. The strategies used to stimulate and preserve motivation on a session-to-session and day-to-day basis remain among key aspects for a successful rehabilitation journey, especially a lengthy one. A frequently used practice to encourage patients to be actively involved during exercises and preserve motivation during therapy is to add a playful component by means of serious games [52].

A serious game is a game that has education or rehabilitation as primary goal without solely prioritizing entertainment. Contrary to commercial “non-specific” video games, serious games are specifically designed for rehabilitation purposes and combine entertainment, attentional engagement and problem solving to challenge function and performance [53]. In recent years, the use of serious games in neurorehabilitation has progressively increased and various types of games have been described in scientific literature [54, 55, 56, 57]. A scoping review by Mubin et al. suggested that developing games for stroke rehabilitation should differ from design methods used for conventional games [58]. However, which should be the design principles to follow in order to optimally develop a serious game in the context of neurorehabilitation remains poorly studied.

Serious games described in scientific literature for stroke rehabilitation present diversified gameplays that depend on the targeted rehabilitation purposes for which the game was designed. Additionally, the game scenario and the game characteristics are usually determined by the technical specifications of the device on which the game is implemented. Serious games can be implemented on various types of systems, such as robotic devices, smartphones, tablets and virtual reality systems (VRS). Figure 9 showcases a series of different devices on which gamified interventions are implemented on. As illustrated, in most cases, serious games are implemented on devices that can be categorized as VRS.

Figure 9a. Touchpad with computer screen interface [52].

Figure 9b. The Rehabilitation Gaming System: tracking through camera with data gloves [53].

Figure 9c. Tabletop touchscreen [54].

Figure 9d. End-effector robot [55].

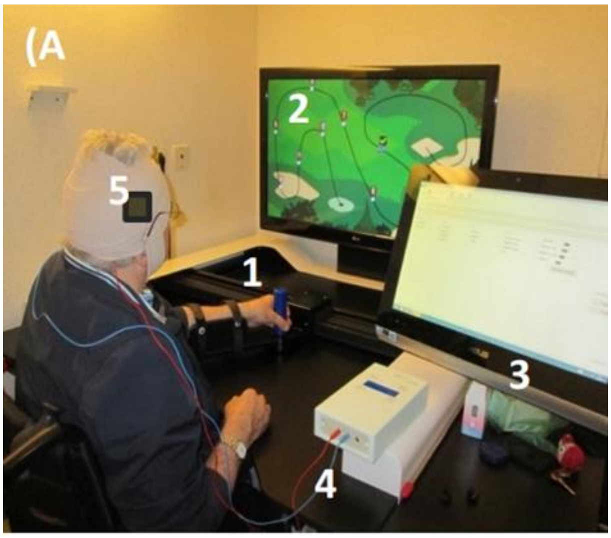


Figure 9e. Head-mounted virtual reality system with controllers [56].

Figure 9f. The Fruit Catcher mini-game: motion-capture system on LCD-monitor [57].

Virtual reality (VR) can be defined as “a computer-based technology that provides the user with a sense of presence in a virtual environment” [59]. It should be noted that “VR” is an umbrella term and that the definition of VR systems (VRS) may vary across literature [60]. This is important to underline because it may influence the outcomes of experimental studies and systematic reviews that evaluate the efficacy of these interventions. A recent meta-analysis demonstrated that VRS specifically designed for rehabilitation lead to better functional outcomes concerning UL motor recovery when compared to systems not specifically developed for rehabilitation [61]. Interestingly, this work also suggested that the effectiveness of VRS specifically developed to enhance motor recovery is dictated by their ability to effectively mobilize recovery mechanisms and stimulate neural plasticity. Consequently, positive effects of interventions in motor rehabilitation may be determined by the degree of adherence to a consolidated set of neurorehabilitation principles previously described in literature and shared among the above mentioned systems [62].

On top of increasing engagement and preserving motivation, serious games may contribute to improve efficacy of rehabilitation interventions and lead to enhanced functional recovery. A recent meta-analysis suggested that adding a gaming component to computerized training leads to better outcomes compared to simple visual feedback [59]. Additionally, due to their inherent characteristics, serious games have the potential to fully exploit the implementation of some specific neurorehabilitation principles, such as the principle of increasing difficulty. For example, task-difficulty during gameplay can be dictated by various parameters such as completion of a task, completion of tasks within a defined time frame, addition of cues or distractors and addition of assistive or resistive forces in the case of serious games implemented on robotic devices. A variety of task-difficulty adaptation mechanisms, aiming to maintain an optimal challenge level during gameplay by modifying game parameters, have been previously described in literature [52]. However, efficacy of these difficulty adaptation strategies remains poorly studied in most cases. Finally, whether adherence to neurorehabilitation principles determines efficacy of broader technology-based interventions, such as serious games, needs to be further investigated.

1.4 Combined rehabilitation of motor and cognitive impairments after stroke and SCI

According to a recent review, it is estimated that up to 80% of stroke survivors present with some form of cognitive impairment [63]. The five types of cognitive impairments that are the most commonly encountered after stroke are: neglect, aphasia, apraxia, loss of executive function and memory disorders [64]. Prevalence and severity of these impairments may vary depending on the characteristics of the studied population and the diagnostic criteria used [63]. Additionally, recent evidence suggests that, in most cases, these impairments should not be regarded as independent entities and that when addressing rehabilitation needs an overlap exists across cognitive domains, motor function and recovery after stroke [64].

Approximately 40% of stroke survivors present hemi-spatial neglect (HSN) [9]. HSN can be defined as a spatial attention deficit to any kind of stimuli (visual, tactile, auditory or mental representation) from the side opposite the brain injury [65]. Presence of HSN is associated with limited functional recovery post-stroke [67]. Therefore, timely identification of the presence of HSN and targeted rehabilitation are essential to maximize functional recovery.

Multiple diagnostic tests have been previously described to identify and assess severity of HSN after stroke. Most of these neuropsychological test batteries consist of paper and pencil tests performed under direct therapist supervision [68, 69]. Alongside the growing use of technology-based interventions, new technology-based methods have also emerged for the identification and the evaluation of the severity of attentional impairments [65]. A recent review has highlighted the need for development of new data driven methods to timely identify cognitive impairments, to track recovery over time, to better understand underlying physiopathology and to adequately select treatment options [66].

In clinical routine, HSN is commonly evaluated and rehabilitated using the healthy arm following stroke. This may be because motor and cognitive impairments are usually addressed separately by different therapists. However, the patient's functional independence is mainly determined by the functional recovery of the paretic limbs. Previous studies have suggested that cognitive-motor dual task training may render additional benefits when compared to other conventional 'single-task' approaches [70]. Indeed, a recent meta-analysis put forward that cognitive-motor dual training for gait rehabilitation leads to better improvements in balance when compared to physical single-task training [71]. Similarly, a randomised controlled trial indicated that dual-tasks exercises might lead to improvements in dual tasks mobility and reduce fall risk in chronic stroke [72]. Another meta-analysis suggested that cognitive-motor dual task training could lead to better improvements in UL motor function when compared to conventional physical or occupational therapy [73]. Beyond motor recovery, it has also been suggested that combined rehabilitation of motor and cognitive impairments could lead to enhanced improvements in cognitive functions [70].

Cognitive-motor dual task training could be delivered using technology-based rehabilitation methods, such as RAT or serious games. Adjunct to conventional methods, RAT offers the possibility of evaluating HSN using the paretic or non-paretic limb and gives access to objective quantifiable data and to rehabilitate simultaneously motor and cognitive impairments [65]. Indeed, recent findings suggest that combined cognitive-motor technology-based rehabilitation after stroke could also lead to better improvements in motor function when compared with time-matched conventional approaches [74]. Additionally, technology-based interventions using robotic devices, VRS and serious games, could complement conventional paper-and-pencil methods for the evaluation and neurocognitive rehabilitation of HSN [65].

All the above elaborated reasons led our research team to develop ROBiGAME, a serious game implemented on the REAplan® robot (Figure 7b) that allows simultaneous rehabilitation of motor and attentional impairments after stroke [75]. ROBiGAME was configurated using a dynamic difficulty adjustment (DDA) mechanism to adapt task difficulty in real time, on a trial per trial basis, by automatically modifying game parameters during training. A detailed explanation of ROBiGAME's characteristics and gameplay is presented in Chapter 2 of this thesis.

Finally, cognitive impairments may also present after spinal cord injury, especially of traumatic origin [76]. According to current estimates, up to 60% of individuals after SCI injury may present with cognitive impairment, with memory impairments and deficits in verbal learning being the most commonly reported types of cognitive impairments [77]. The pathophysiological mechanisms underlying these impairments remain poorly understood to this day [76]. Some authors suggest that cognitive impairments after SCI share similarities in dysfunction of central nervous system pathways leading to motor impairments [19]. In context of trauma, it has been highlighted that head injuries often accompany SCI which could partially explain the presence of cognitive impairment. Also, the presence of neuroinflammation and neurodegeneration following SCI may contribute to the development of cognitive impairment and some studies have linked the decrease in physical activity levels following SCI with the development of neurocognitive impairments [76].

In current clinical practice, cognition is usually not addressed in the context of SCI, partially due to the lack of appropriate tools targeting evaluation and rehabilitation of these functions after SCI, as highlighted by a recent review [77]. However, impairments in attention, memory or learning may directly influence rehabilitation efficacy and consequently functional recovery outcomes. The complex interaction between cognition and motor function after SCI remains a poorly investigated field.

1.5 Objectives of this PhD thesis

As indicated in the above sections, several gaps remain in literature regarding the use of robotic devices and serious games in motor and cognitive neurorehabilitation.

It is important to note that, since this PhD project started in October 2019, the research work initially planned was heavily impacted by the COVID-19 pandemic and, therefore, the objectives of this thesis needed to be adapted to the circumstances. Specifically, it was not possible to conduct a multicentre, single-blind, randomized controlled pragmatic trial assessing the ROBiGAME therapeutic efficacy due to hospital's restraint policy. The COVID-19 pandemic gave us the opportunity to identify that efficacy of serious games for UL rehabilitation after stroke had never been explicitly reviewed. Consequently, we decided to modify the initial plan of this project and conduct a systematic review with meta-analysis in order to fill this knowledge gap.

This PhD project had two main objectives and two complementary ones.

The primary objective of this PhD thesis was to clinically validate ROBiGAME's DDA mechanism in order to demonstrate that combined motor-cognitive rehabilitation after stroke, through individualized levels of difficulty, is feasible. Additionally, by presenting a novel approach to perform clinical validation, we wanted to highlight that mechanisms used to adapt task-difficulty using technology-based rehabilitation should undergo validation before use in clinical settings. Indeed, in scientific literature, various ways to perform task-difficulty adaptation have been previously described for RAT and serious-game training after stroke [43, 52]. However, in most cases, the way difficulty adaptation is performed during training concerns exercises solely targeting motor recovery and remains vaguely described. Additionally, to this day, only a handful of studies have focused on combined motor-cognitive rehabilitation approaches using new technologies, without describing how task-difficulty should be dictated in combined approaches especially concerning cognitive aspects. Findings related to this work are elaborated in the first section of this manuscript (Chapter 2).

The secondary objective of this PhD thesis was to assess the efficacy of serious games to rehabilitate the UL motor function and activity following stroke. In this regard, we conducted a systematic review with meta-analysis focusing on adults after stroke. As mentioned above, serious games can be implemented on different types of technological devices. Although previous reviews have studied efficacy of interventions based on the technological device used, no systematic work had previously reviewed efficacy of serious games as a distinct intervention. Additionally, we explored what are the characteristics of serious games that may influence their efficacy as interventions. In order to do this, we assessed whether a higher adherence to a consolidated set of 11 neurorehabilitation principles enhances efficacy of interventions in form of serious games for UL rehabilitation after stroke. This work is reported in Chapter 3.

Finally, in order to investigate other dimensions of this field of research and open perspectives for future applications of our findings covered in Chapters 2 & 3, this PhD thesis had two complementary objectives. First, another systematic review with meta-analysis was conducted in order to evaluate efficacy of interventions in form of self-rehabilitation after stroke. Indeed, technology-based interventions complement conventional rehabilitation treatments and offer opportunities in terms of self-rehabilitation. Findings and related observations to this work are presented in Chapter 4. Second, technological improvements in hardware and software dictate the rhythm at which technology-based rehabilitation interventions evolve and expand to new applications in clinical practice. For this reason, we decided to conduct a systematic review to evaluate whether the use of WPE for gait training is a feasible and safe intervention after tetraplegia due to SCI. In this work, we also assessed whether walking ability improved after gait training using WPE and whether this treatment leads to additional health benefits regarding gastro-intestinal, urological, or musculoskeletal systems. Detailed findings related to this work are presented in Chapter 5.

In the last section of this PhD thesis (Chapter 6), we put forward the principal findings related to this work, discuss how our findings can be integrated in recent literature and expand current knowledge, suggest how current clinical practices could be influenced by our results and propose future research questions that should be investigated.

CHAPTER II – Clinical validation of an individualized auto-adaptative serious game for combined cognitive and UL motor robotic rehabilitation after stroke

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Published in Journal of Neuroengineering & Rehabilitation 2025;22(1):10.

doi:10.1186/s12984-025-01551-w

2.1 Abstract

Background: Intensive rehabilitation through challenging and individualized tasks are recommended to enhance UL recovery after stroke. RAT and serious games could be used to enhance functional recovery by providing simultaneous motor and cognitive rehabilitation.

Objective: The aim of this study is to clinically validate the DDA mechanism of ROBiGAME, a robot serious game designed for simultaneous rehabilitation of motor impairments and HSN.

Methods: A proof of concept, with 24 participants in subacute and chronic stroke, was conducted using a 5-day protocol (two days were dedicated to assessment and three days to consecutive training sessions). Participants performed three consecutive ROBiGAME sessions during which overall task difficulty was determined through simultaneous DDA of motor and attentional parameters. Relationships between clinical and robotic assessment scores with respective task-difficulty parameters were analysed using a multivariate regression model and a principal component analysis.

Results: Game difficulty rapidly (within approximately thirty minutes) auto-adapted to match individual impairment levels. The relationship between task-difficulty parameters with motor (Fugl Meyer Assessment: $r=0.84$ $p<0.05$) and with attentional impairments (Bells test total omissions: $r=0.617$ $p<0.05$) showed that task-difficulty during RAT adapted to each participant's degree of impairment. Principal component analysis identified two data subsets determining overall task-difficulty, one subset for motor and the other for cognitive functional evaluation scores with respective task-difficulty parameters.

Conclusions: This proof of concept clinically validated a DDA mechanism and showed how task-difficulty adequately adapted to match individual degrees of impairment during RAT after stroke. ROBiGAME provided simultaneous motor and attentional exercises with parameters determining task-difficulty strongly related with respective clinical and robotic evaluation scores.

Individualized levels of game difficulty and rapid adjustment of the system suggest implementation in clinical practice.

Registry number: This study was registered at ClinicalTrials.gov (NCT02543424).

Key terms: neurorehabilitation, stroke, cognitive rehabilitation, robot-assisted therapy, motor learning, serious games.

2.2 Background

Context

Each year more than 13 million people worldwide have a stroke, with approximately two-thirds having persistent UL paresis and one-third presenting with HSN [9, 74]. Intensive rehabilitation using challenging and individualized tasks enhance functional recovery after stroke [21]. Emerging techniques promote intensive rehabilitation and allow simultaneous motor and cognitive training, complementing conventional approaches.

Task difficulty adaptation during robotic rehabilitation

Recent guidelines recommend RAT to improve UL strength, function and activities of daily living after stroke [36]. A review on control strategies, presented various types of task-difficulty adaptation mechanisms described in scientific literature for robotic neurorehabilitation [78]. Among these adaptive mechanisms, some are configured to automatically adjust task-difficulty using data derived from the robotic device as input to system decision-making [79]. Most commonly used computerized systems often rely on "assist-as-needed" guidance algorithms to adjust motor task-difficulty [78]. However, the way these systems' effectiveness is validated varies in scientific literature and remains vaguely described in many cases [43]. More specifically, it would be worthwhile to assess the pertinence of the decisions made by the system during training. Are the parameters determining task-difficulty during RAT well adapted to the functional profiles of subjects after a stroke?

Dynamic difficulty adjustment (DDA) during serious-game training

Serious games also constitute an effective approach to stimulate UL recovery after stroke. RAT can be combined to serious games to continuously and automatically adapt task-difficulty to match individual participants' impairments and immediate performance during training [58]. Depending on device and game characteristics, different types of task-difficulty adaptation mechanisms have been previously described for serious games in stroke rehabilitation [52]. For example, serious games implemented on virtual reality systems can adapt game difficulty using preestablished increments, configured at the beginning of each session by a therapist [80]. Other virtual reality tools allow progressive difficulty adjustment based on individual performance [81]. This type of difficulty regulation mechanism, known as dynamic difficulty adjustment (DDA), has also been described for serious games implemented on robotic systems [82]. The objective of DDA mechanisms is to adjust task-difficulty automatically, in real time, according to user performance, creating feasible, yet challenging tasks, keeping the game in constant balance [81, 82].

DDA mechanisms present two main advantages. First, game characteristics dynamically adjust to match participants' individual degree of impairment and performance in order to maintain an optimal challenge according to neurorehabilitation principle of increasing difficulty [62]. Secondly, DDA mechanisms lead to individualised levels of task-difficulty which could enhance human performance by maintaining a balance between motivation and learning. According to the concept of flow, in order to preserve motivation during training, task-difficulty should match participants' skill levels and should avoid extremes (i.e. exercise through tasks that are not too easy nor too difficult) [82]. Our team developed ROBiGAME [83], a serious game implemented on an end-effector rehabilitation robot using a DDA mechanism, detailed below.

Combining motor and cognitive rehabilitation after stroke using robotic devices

In research and clinical practice, motor and cognitive impairments are usually addressed separately by different therapists. Additionally, most robotic devices are designed to solely target motor rehabilitation (i.e., not additionally including cognitive exercises) [84].

It has been suggested that combined cognitive-motor rehabilitation after stroke could lead to better improvements in motor function when compared with time-matched conventional approaches [74]. Although cognitive training constitutes an essential part of adult stroke rehabilitation, a recent systematic review underlined that cognitive exercises are insufficiently incorporated into robotic devices for combined rehabilitation in the stroke population [85]. Another systematic review identified only one study for robot-assisted cognitive training after stroke [86]. This review also highlighted that one of the main challenges of robotic rehabilitation for cognitive training remains personalisation of task-difficulty using RAT systems [86]. Indeed, participants' impairment severity and functional deficits vary widely after stroke, leading to differences concerning rehabilitation needs and objectives.

In this proof of concept, we study the DDA mechanism of ROBiGAME, a novel robotic gamified approach, that allows combined UL motor and cognitive rehabilitation for attentional impairments following stroke.

Objectives and hypothesis

The primary objective of this proof of concept was to clinically validate ROBiGAME's DDA mechanism. We evaluated whether parameters determining task-difficulty during gameplay adapted to individually match participants' degree of motor impairments and/or HSN following stroke. We hypothesized that ROBiGAME’s DDA mechanism would lead to a different level of difficulty corresponding to each participant’s degree of impairment.

Secondary objectives examined whether characteristics during gameplay (i.e., number of targets, number and position of visual distractors presented on screen, etc.), defining task difficulty, would rapidly adapt to reach an individualized level of difficulty.

2.3 Methods

Ethics committee

This proof of concept was approved by the clinical ethics committee of UCLouvain (Belgium). The study protocol was registered at ClinicalTrials.gov (NCT02543424). Participants signed an informed consent form before testing.

Study design

This study was conducted using a 5-day experimental protocol. During the first two days, neurological impairments were evaluated using standardized clinical and robotic assessments. Then, on the three remaining days, each participant completed a daily 45-minute session of RAT playing ROBiGAME. All sessions were performed at the Cliniques universitaires Saint-Luc (Brussels, Belgium).

Participants

Recruitment took place during inpatient and outpatient rehabilitation. Participants were enrolled according to the following inclusion criteria: a first stroke diagnosis confirmed by computed tomography or magnetic resonance imaging, clinical stability, participants in subacute or chronic phase after stroke [87], presence of UL hemiparesis with preserved ability to voluntarily move the robot's end-effector, an ability to understand instructions and carry out tests. Ability to understand instructions was evaluated in collaboration with the clinical rehabilitation team in charge of therapy for each participant. Participants were excluded when they had a stroke located in the brain stem or cerebellum or presented with any other associated neurological or orthopaedic illness limiting UL function.

Data collection

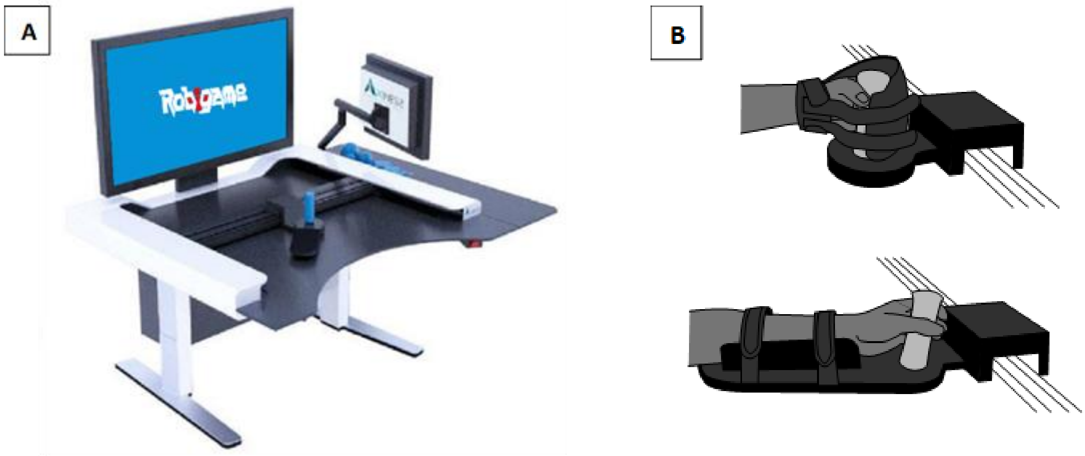
Motor and cognitive clinical evaluation

Participants' cognitive status regarding presence of HSN was assessed using the Bells and Apples tests, two paper-and-pencil tests commonly used in clinical practice [88]. UL motor impairments were clinically assessed using standardized rating scales according to recent recommendations for neurorehabilitation trials [89]. UL motor control was evaluated with the computerized and adaptive testing system of the Fugl-Meyer Assessment (FMA) for the Upper Extremity (FMA-UE) [90]. Gross manual dexterity was assessed using the Box and Block test [91]. Activity limitations were evaluated with the Action Research Arm Test (ARAT) [92]. When applicable, degrees of participants impairments and limitations were categorised as mild, moderate and severe.

The REAplan® robot

The REAplan® (Axinesis, Wavre, Belgium), illustrated in Figure 1A, is a distal end-effector robot that was used in this study to conduct robotic assessments and to play ROBiGAME sessions. REAplan® allows movements of the UL by mobilization of the hand in the horizontal plane, in different modes (active, active-assisted, passive, resistive) [27]. This robot, equipped with force and position sensors, recorded the position of the handle and the force exerted on the handle, with a frequency of 125 Hz. During training, the robot can provide motor assistance to help the participant complete the desired movement or can apply resistive force to disturb the participants' movements, according to a predetermined set of rules described in previous work [75]. All study participants were positioned in a standardised way during evaluation and sessions. A gutter was used to stabilize the participant's paretic wrist and forearm (Figure 1B). If necessary, the participant's hand was attached with a glove to the distal end-effector (Figure 1B).

Figure 1. Illustration of the REAplan® robot [31], ROBiGAME's display [75] and schematic diagram of ROBiGAME's Dynamic Difficulty Adjustment mechanism.



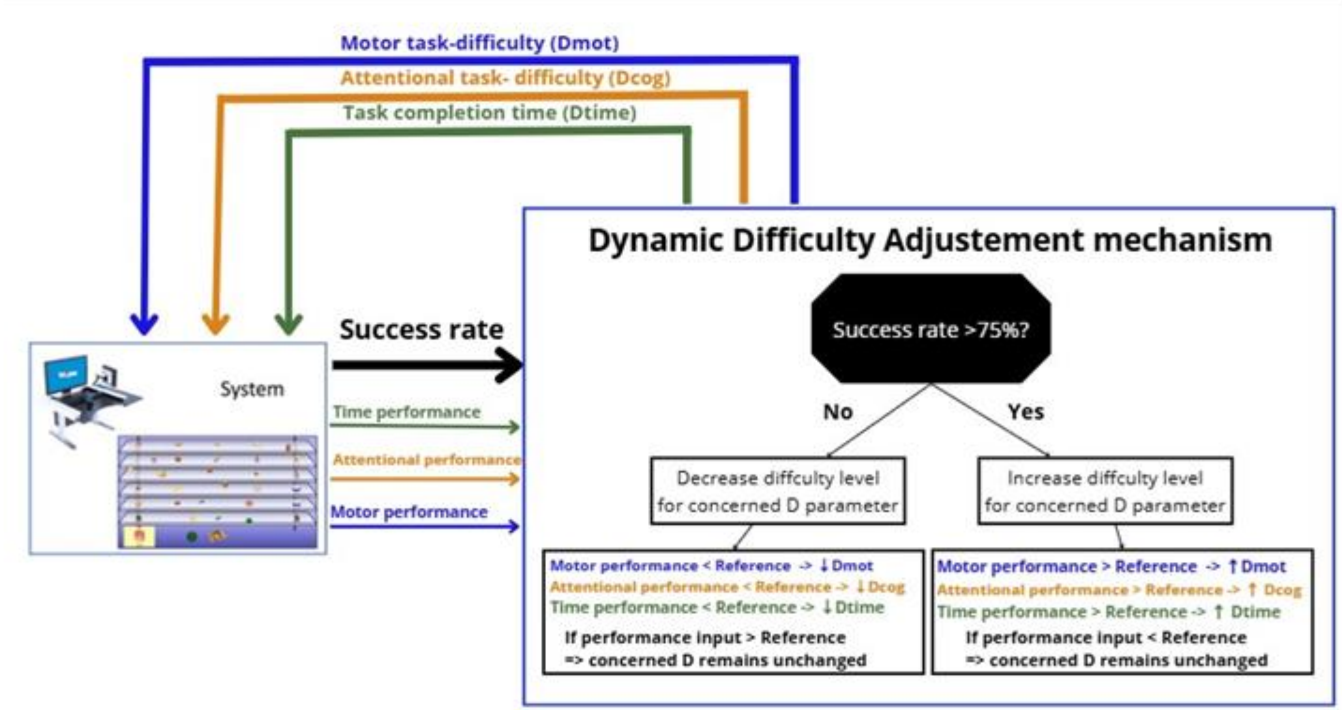
A: Illustration of the REAplan® robot (Axinesis, Wavre, Belgium).

B: Positioning of the hand in the glove and the forearm in the gutter.

C

C: Four examples of the robotic interface, through the LCD screen illustration, during a ROBiGAME session corresponding to the environment and configuration of the game at different time points.

D



D: Schematic diagram of ROBiGAME's Dynamic Difficulty Adjustment mechanism

Motor and cognitive robotic evaluation

In addition to clinical evaluation, motor and attentional impairments were assessed using the REAplan® robot. UL kinematic indexes (straightness and smoothness) and isometric, pushing and pulling, forces with elbow extended at 90° were retained. Straightness index corresponded to the ratio between movement amplitude and path length covered by the participant. Smoothness index was the ratio between the mean and peak velocities of participant's movements, with a ratio closer to 1 indicating rectilinear paths and smoother movements [27].

In line with a recent systematic review suggesting the use of multi-test methods to detect hemi-spatial neglect [9], a robotic test was also performed in addition to the two paper-and-pencil tests described above. The MonAmour test was developed and validated on the REAplan® device for evaluation of allocentric and egocentric HSN [65]. The MonAmour test gives access to various parameters including total mean reaction time, difference in reaction time between contralesional and ipsilesional space, number of total omissions and differences in total omissions between contralesional and ipsilesional space.

ROBiGAME

ROBiGAME is a serious game implemented on the REAplan® robot that allows simultaneous rehabilitation of motor and attentional impairments after stroke [83]. Our team developed a DDA mechanism that allows this serious game to adjust task difficulty in real time, on a trial per trial basis, by automatically modifying game parameters during training.

During the game scenario (Figure 1C), a series of planar reaching movements were performed to complete tasks. For each task, the level of difficulty was defined by exercise / game characteristics, such as target position, level of robot assistance / resistance and the number of visual distractors presented on the screen (Figure 1C). These characteristics continuously adjusted, using a DDA mechanism described below, to match participant's performance during game play. The objective was to successfully complete as many tasks as possible by reaching a specified number of targets within a desired time frame.

The DDA uses a preestablished set of rules to adjust task-difficulty to the level of individual participant performance and impairment by modifying the parameters presented in Table 1. Each parameter varies independently and determines motor task-difficulty (Dmot), attentional task-difficulty (Dcog) and task completion time (Dtime). In order to challenge the player, overall task-difficulty is continuously modified during gameplay without reaching a constant value. Task-difficulty parameters (D) oscillate from 0 to 1. A 'D score' closer to 1 indicates a higher level of difficulty. Each task-difficulty parameter (D) is respectively paired with participants' performance parameters (output of the game). Performance parameters are compared in real-time to predefined normative data obtained in an age-matched stroke population [93]. Game task-difficulty is adapted according to the game success rate. Success rate is measured by averaging results over the ten most recently performed tasks (using a dynamic sampling window for each subsequent performed task). If an exercise is completed within the desired timeframe, it is considered as a successful completion of the task. For example, if over the last 10 tasks, a patient succeeded on 7 tasks, then the success rate is determined as 70% (indicating that the individualised task-difficulty parameters allowed the player to successfully complete 7/10 tasks). In accordance with scientific literature, the 10 task success rate is compared to a target reference success rate set at 75% [61, 93]. It is suggested that keeping success rates within an optimal range at approximately 75 % enhances human performance by maintaining a balance between motivation and learning [94]. The comparison between the success rate during training and the reference success rate determines whether the difficulty level of the game should be increased or decreased. If the success rate over the previous 10 tasks is higher than 75%, it indicates that task-difficulty of corresponding parameters is too low (too easy) and difficulty is increased. On the other hand, if the success rate over the previous 10 tasks is below 75%, it indicates that the task-difficulty of corresponding parameters is too high (too difficult), and the difficulty level is decreased. By modifying these parameters and the related game characteristics described in table 1, ROBiGAME regulates difficulty of tasks performed during training. A detailed scheme of ROBiGAME's DDA mechanism is presented in Figure 1D.

For this study, all task-difficulty parameters were set at the lowest value (0) at the beginning of the first session. Then, throughout sessions, adaptation of each parameter occurred automatically. For each participant, evolution of values of different parameters was recorded during all sessions.

Table 1. ROBiGAME's parameters.

Task-difficulty parameters (D)	***Game characteristics*** that vary to adapt task-difficulty
D_{mot} = motor task-difficulty	• Longitudinal assistance or resistance force provided by the robot
D_{cog} = cognitive task-difficulty	• Total number of targets • Target position • Attentional load = number of distractors • Number of cognitive cues provided
D_{time} = task completion time difficulty parameter	• Total time available to complete a series of tasks
Participants' performance parameters	
Motor performance = reflects velocity (cm.s^{-1}) of movements performed by the patient in the horizontal plane.	
Attentional performance = reflects the patients' reaction times by taking into consideration attentional load and salience of the cognitive cues.	
Time performance = reflects the total time needed for task completion.	
Game success rate*:* the game success rate varies from 0 to 100%.	

Abbreviations: D= task-difficulty parameters.

Primary and secondary objectives and outcomes

The primary objective of this work was to study the relationship between clinical evaluation scores and the level of task-difficulty reached at the end of three game sessions (mean of the last 10 performed tasks), for motor and attentional parameters (Dmot and Dcog). We investigated whether parameters determining task-difficulty (D) correlated to participant's degree of impairment as a primary outcome. We hypothesized a negative relationship showing that with reduced degree of impairment (relative to norms), the level of game difficulty would increase for corresponding parameters, making the game more difficult. Also, we studied which clinical evaluation scores explain the level of task-difficulty reached at the end of all sessions (mean of the last 10 performed tasks) for corresponding motor and attentional parameters.

Secondary objective was to examine whether characteristics during gameplay rapidly reach an individualized level of difficulty corresponding to each participants' degree of impairment. We considered adjustment to be rapid when it occurred after approximately thirty-minutes, corresponding to completion of 15 to 20 tasks. As a secondary outcome, we studied the correlation between the reached motor task-difficulty after completion of 20 tasks (mean of the first 20 performed tasks) with the motor task-difficulty reached at the end of all sessions (mean of the last 10 performed tasks).

Data analysis

Statistical analyses were performed using the SPSS Statistics software (IBM, version 27). The normality and equality of variances were checked by QQ-Plot graphic representation and Levene's test respectively [95]. Statistical significance level was set at $P < 0.05$ for all analyses.

To explore the structure of our data regarding functional assessment scores and levels of difficulty reached during the game, a principal component analysis was performed [96]. Principal component analysis included clinical and robotic (motor and attentional) evaluation scores and mean levels of task-difficulty (Dmot, Dcog) at the end of the three sessions. The number of generated principal components was selected based on scree plot interpretation and Kaiser criterion [97].

Two multiple linear regression models were computed to study separately the relationship between level of motor or attentional task-difficulty reached at the end of all sessions (with Dmot or Dcog set as dependent variables) and respective clinical/robotic evaluation scores regarding motor or attentional impairments (as explanatory variables). A stepwise selection was performed in order to identify the most pertinent explanatory variables [98]. When applicable, additional simple linear regression analyses were performed to study the relationship between Dmot or Dcog and the remaining variables.

A repeated measures ANOVA was conducted to analyse whether levels of game motor difficulty reached after completion of 20 first tasks differed in comparison to the value reached at the end of all sessions (mean of the last 10 performed tasks). We estimated that a sample size of 21 participants would be needed for this analysis, using an a=0.05 and b=0.80 [99].

2.4 Results

All 24 participants recruited for this study successfully completed all evaluations and training sessions with full collaboration and no adverse events. Characteristics of participants are presented in Table 2. Approximately half of them presented with HSN (11 out of 24), according to assessment scores on the MonAmour test [65].

Table 2. Characteristics of study participants.

n = 24	μ ±SD or absolute value
Age (years)	61 ±12.1
Sex (M/F)	12/12
Dominant arm (R/L)	22/2
Type of stroke (I/H)	22/2
Time since stroke (weeks)	6 ±4.1
Affected arm (R/L)	11/13
Hemispatial neglect [a]	11
NIHSS [b]	11 ±6.1
Exteroceptive sensitivity (P/A) [c]	15/9
Proprioceptive sensitivity (P/A) [c]	16/8

Abbreviations: n= total number of participants in this study, μ= mean value, SD= Standard Deviation, M= male, F= female, I= ischaemic, H= haemorrhagic, NIHSS= National Institute of Health Stroke Scale, R= right, L= left, P= preserved, A= altered.

[a] Presence of hemispatial neglect according to MonAmour test.

[b] Assessment at the day of admission in the neurology department.

[c] According to NIHSS.

Clinical and robotic evaluation scores for motor and attentional impairments are summarized in Table 3. Concerning motor aspects, mean FMA-UE scores were 67% (±27.3%) and mean ARAT scores were 35 (±22.8), corresponding respectively to a moderate level of impairment and activity limitation according to the ICF-WHO model. Participants had FMA-UE scores ranging from 14% to 99% and ARAT scores ranging 0 to 57, covering a wide range of motor impairment severity and activity limitation (mild, moderate and severe). Concerning attentional impairments, number of omissions asymmetry ranged from 0 to 33 and mean reaction time asymmetry was of 380 ms (?99 ms) which corresponds to different participants profiles' regarding presence of hemi-spatial neglect (i.e., number of omissions asymmetry). The heterogeneity of our sample in terms of types and severity of motor and attentional impairments is further illustrated in supplementary Figure 1 (S1A, S1B, S1C).

Table 3. Clinical & robotic functional assessments of participants and ROBiGAME difficulty scores.

n=24	**Motor** aspects		**Attentional** aspects	
Clinical assessments		*μ ±SD*	**Bells Test**	*M [min. – max.]*
	FMA-UE (%)	67 ±27.3	Total omissions (n)	2 [0 – 27]
	ARAT (/57)	35 ±22.8	Omissions asymmetry (n)	0 [-2 – 8]
	Box and Block Test (block/min)	20 ±19.1	**Apples Test**	
			Total omissions (n)	2 [0 – 42]
			False positive asymmetry (n)	2 [-3 – 34]
Robotic assessments		*μ ±SD*	**MonAmour Test** []	*M [min. – max.]*
	Force (N) pulling (flexion)	100 ±48.0	Total omissions (n)	0 [0 – 67]
	Force (N) pushing (extension)	88 ±55.0	Omissions asymmetry (n)	0 [0 – 33]
	Kinematic indexes		False positive asymmetry (n)	0 [-3 – 2]
	Velocity (m.s^{-1})	9.4 ±6.3		*μ ±SD*
	Straightness	0.92 ±0.1	Total Mean reaction time (ms)	2313 ±96
	Smoothness	0.45 ±0.2	Mean reaction time asymmetry (ms)	380 ±99
ROBiGAME's difficulty parameters and success rate		*μ ±SD*		*μ ±SD*
	D_{mot} *after one game session*	0.69 ±0.3	**D_{cog}** *after one game session*	0.42 ±0.4
	after three game sessions	0.76 ±0.3	*after three game sessions*	0.61 ±0.4
	D_{time}		*after one game session*	0.71 ±0.2
			after three game sessions	0.73 ±0.2
	Success rate		*after three game sessions*	0.76 ±0.1

Abbreviations: n= total number of participants in this study, μ ± SD =mean value ± Standard Deviation, *Median [minimum – maximum or range]*, **FMA-UE= Upper Extremity subscale of the Fugl-Meyer Assessment, %= score expressed in percentage, ARAT= Action Research Arm Test, N= Newtons, ms= milliseconds; m.s^{-1}= metres per seconds; D_{mot} = motor task-difficulty parameters; D_{cog} = attentional task-difficulty parameters; D_{time} = task completion time parameter.**

Figure S1A. Participants' initial MonAmour test scores (total omissions asymmetry) against UE-FMA scores.

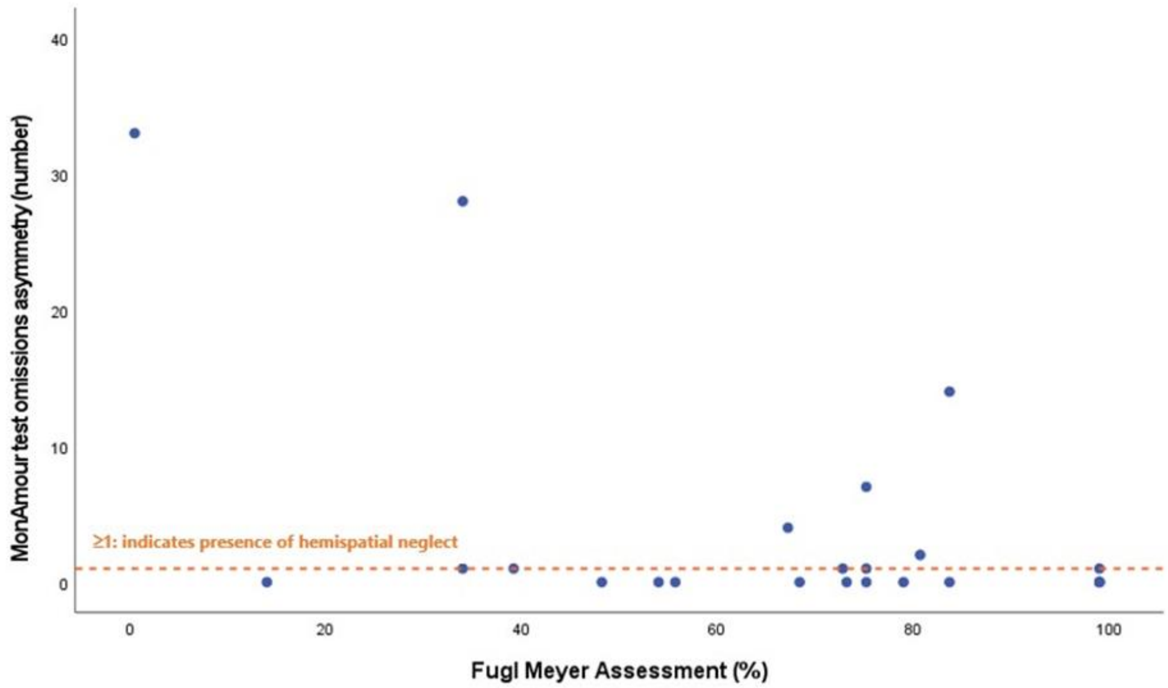


Figure S1B. Participants' initial MonAmour test scores (total omissions asymmetry) against Bell's test scores (total omissions).

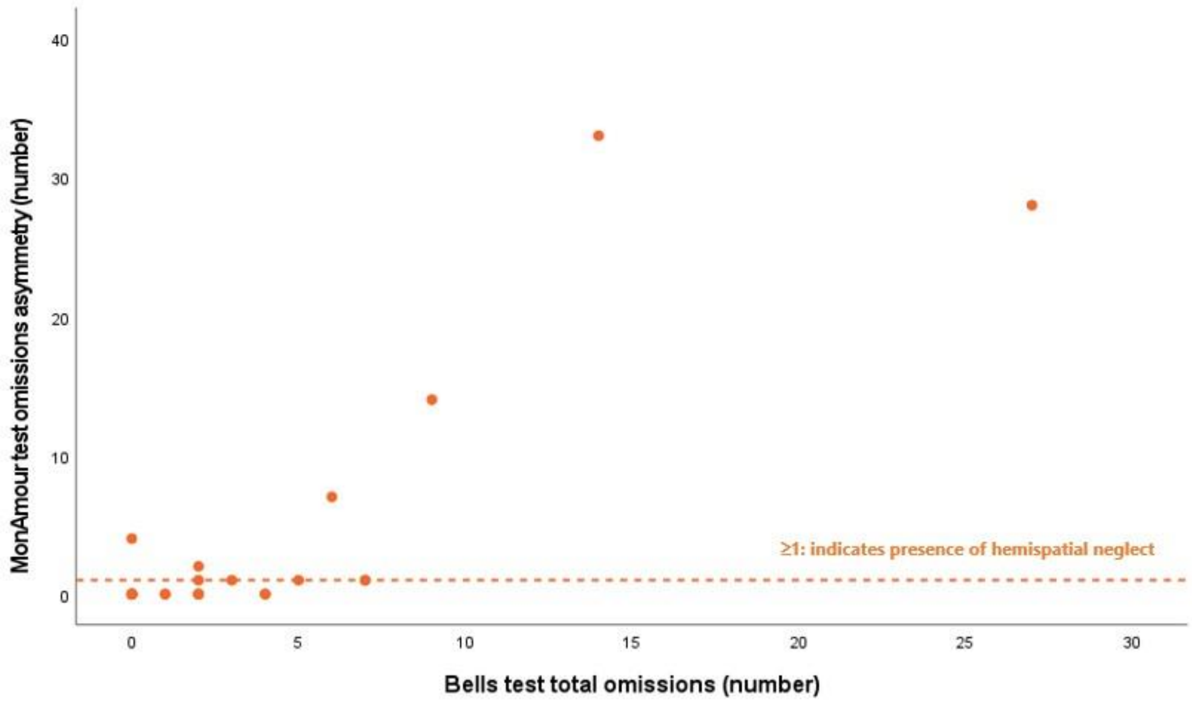
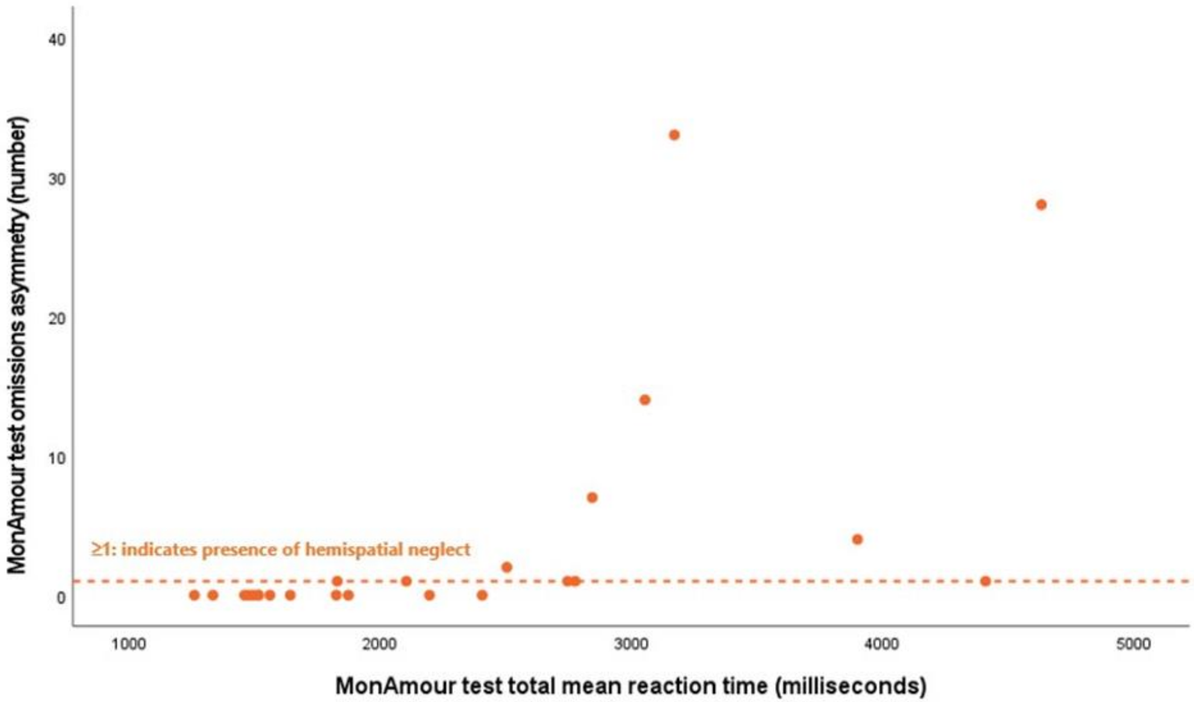
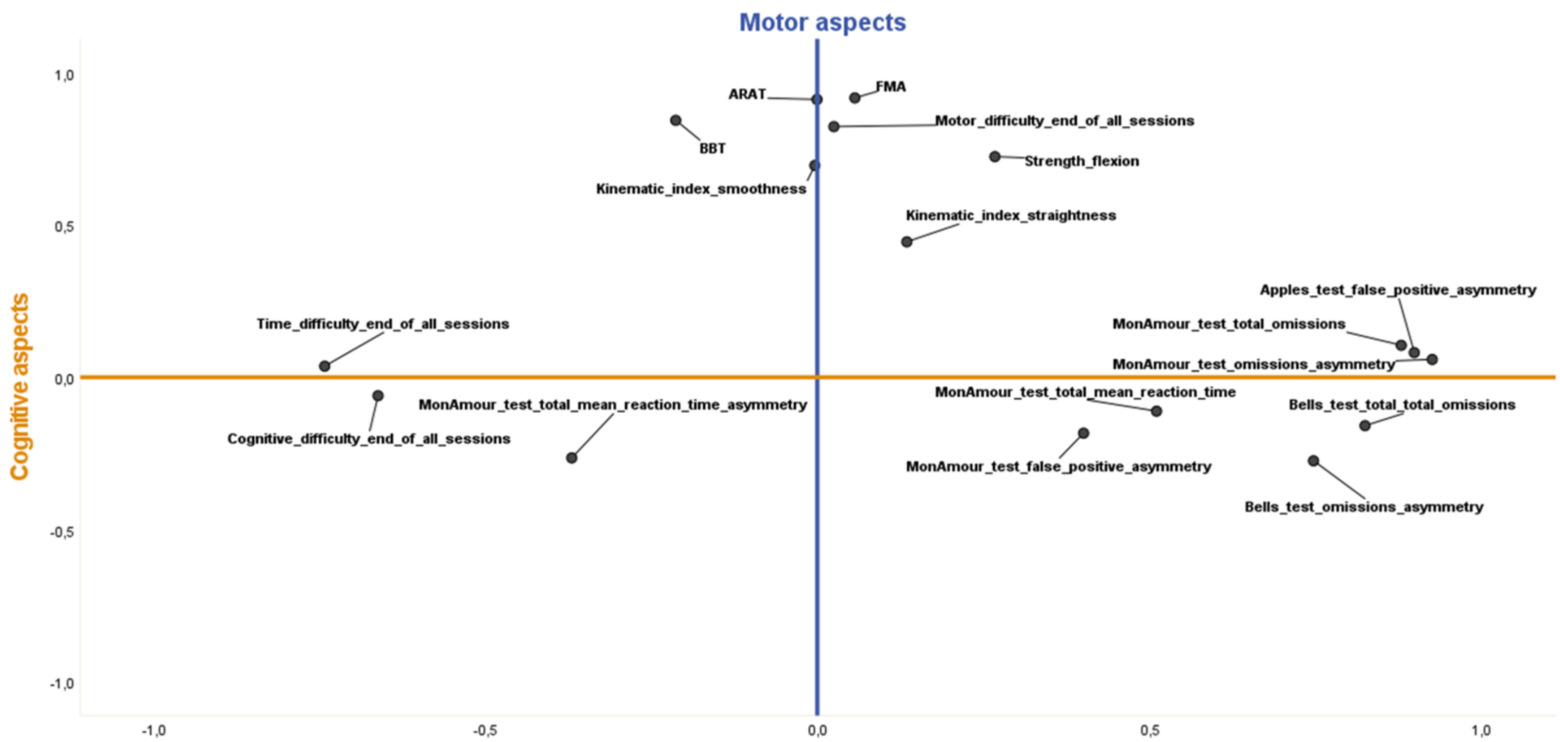


Figure S1C. Participants' initial MonAmour test scores: total omissions asymmetry against total mean reaction time.



Main results of the principal component analysis are illustrated in Figure 2. A total of 2 components were retained after scree plot interpretation (supplementary Figure 2) and application of Kaiser criterion (supplementary Table 1). Aspects related to attentional impairments were retained on the first principal component and aspects related to motor impairments on the second. Attentional difficulty (Dcog) and task completion time parameter (Dtime) reached at the end of all training sessions, along with total mean reaction time asymmetry in the MonAmour test, inversely correlated with principal component 1. Also, the level of attentional difficulty (Dcog) and the task completion time parameter (Dtime) were negatively related to attentional impairments evaluation scores on principal component 1. Motor task-difficulty reached at the end of all training sessions along with motor evaluation scores highly correlated with principal component 2.

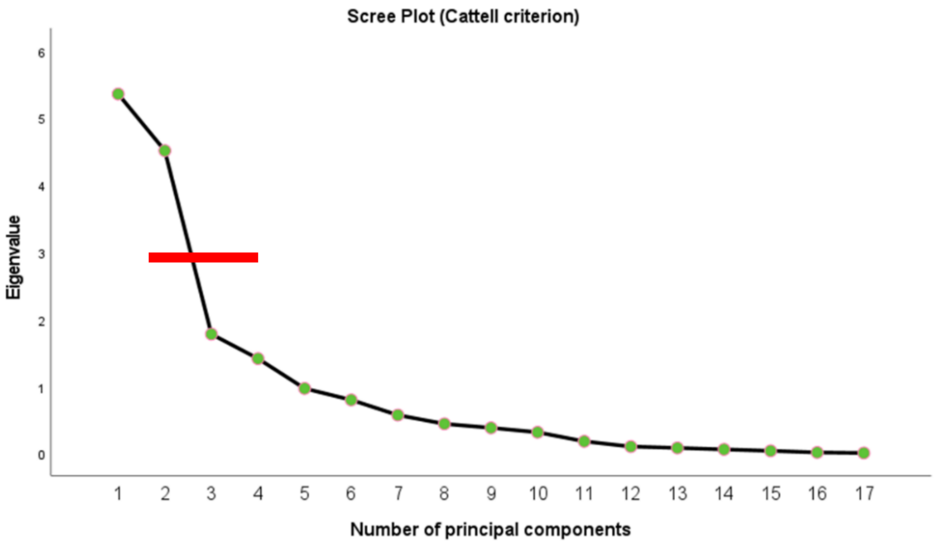
Figure 2. Principal component analysis illustrated in graphic and table form.



	Component 1 Cognitive aspects	Component 2 Motor aspects
Fugl Meyer Assessment - Upper Extremity		**0,917**
Action Research Arm Test		**0,912**
Box and Block test		**0,844**
Motor difficulty reached at the end of all sessions		**0,823**
Arm flexion strength		**0,724**
Kinematic index smoothness		**0,695**
Kinematic index straightness		**0,445**
MonAmour test omissions asymmetry	**0,925**	
Apples test false positive asymmetry	**0,898**	
MonAmour test total omissions	**0,878**	
Bells test total omissions	**0,824**	
Bells test omissions asymmetry	**0,746**	
MonAmour test total mean reaction time	**0,510**	
MonAmour test false positive asymmetry	**0,400**	
MonAmour test total mean reaction time asymmetry	**-0,371**	
Cognitive difficulty reached at the end of all sessions	**-0,663**	
Time difficulty reached at the end of all sessions	**-0,743**	

Two components were retained: data regarding cognitive aspects were retained on component 1 (horizontal) represented in orange, data regarding motor aspects were retained on component 2 (vertical) represented in blue. Correlation coefficients of each variable with respective component are also annotated.

Figure S2. Principal component analysis: scree plot graphic representation.



Supplementary Table 1. Principal component analysis: total variance explained (Kaiser criterion).

	Initial Eigenvalues			*Extraction Sums of Squared Loadings*		
Component	Total	% of Variance	Cumulative %	*Total*	*% of Variance*	*Cumulative %*
1	**5,353**	**31,491**	**31,491**	***5,353***	***31,491***	***31,491***
2	**4,510**	**26,530**	**58,020**	***4,510***	***26,530***	***58,020***
3	1,776	10,449	68,470			
4	1,412	8,307	76,776			
5	0,967	5,689	82,465			
6	0,797	4,686	87,151			
7	0,571	3,356	90,507			
8	0,440	2,589	93,096			
9	0,380	2,237	95,333			
10	0,315	1,851	97,185			
11	0,179	1,055	98,240			
12	0,101	0,596	98,836			
13	0,081	0,478	99,314			
14	0,059	0,350	99,664			
15	0,038	0,222	99,886			
16	0,014	0,081	99,966			
17	0,06	0,034	100,00			

Results of the two multiple linear regression models, computed separately for motor and attentional aspects, are respectively illustrated in supplementary Tables 2 and 3. After removal of non-essential explanatory variables, using a stepwise selection process and co-linearity verification, only one explanatory variable was selected in each model. FMA-UE score was retained for the multiple linear regression model regarding motor aspects (R^2 = 0.710; $p<0.05$) and Bells test total omissions regarding the multiple linear regression model for attentional aspects (R^2 = 0.387; $p<0.05$). An additional simple linear regression was then separately computed with each one of the remaining variables, one motor and one attentional, to further study the relationship between evaluation scores and levels of game difficulty. These relationships are graphically illustrated in Figure 3 (graph B for motor aspects and graph D for aspects related to cognition).

Supplementary Table 2. Multiple Linear Regression model for motor aspects.

Model summary

R	R²	Adjusted R²	Standard Error of the Estimate
0,843[a]	0,710	0,696	0,14036

a. Predictors: (Constant), FMA

ANOVA

	Sum of squares	DF	Mean square	F	Sig
Regression	1,012	1	1,012	51,381	0,000[b]
Residual	0,414	21	0,020		
Total	1,426	22			

a. Dependent Variable: Motor difficulty reached at the end of all sessions
b. Predictors: (Constant), FMA

Coefficients

	Unstandardized Coefficients		Standardized coefficients			Collinearity statistics	
	B	Std Error	Beta	t	Sig	tolerance	VIF
(Constant)	0,130	0,093		1,402	0,175		
FMA	0,009	0,001	0,843	7,168	0,000	1,000	1,000

a. Dependent variable: Motor difficulty reached at the end of all sessions

Excluded Variables

	Beta in	T	Sig	Partial correlation	Tolerance	VIF	Minimum Tolerance
ARAT	0,186[b]	0,869	0,395	0,191	0,304	3,287	0,304
Box and Block test	-0,084[b]	-0,471	0,643	-0,105	0,449	2,228	0,449
Arm flexion (N)	0,203[b]	1,259	0,222	0,271	0,515	1,943	0,515
Arm extension (N)	0,270[b]	1,668	0,111	0,349	0,487	1,227	0,815
Straightness	0,032[b]	0,237	0,815	0,053	0,815	1,227	0,815
Smoothness	-0,033[b]	-0,214	0,833	-0,048	0,625	1,601	0,625

a. Dependent Variable: Motor difficulty reached at the end of all sessions
b. Predictors in the Model: (Constant), FMA

Abbreviations: FMA, Fugl Meyer Assessment; **ANOVA**, Analysis of Variance; **Std**, Standard; **Sig**, significance; **DF**, Degrees of Freedom; **VIF**, Variance Inflator Factor; **ARAT**, Action Research Arm Test.

Supplementary Table 3. Multiple Linear Regression model for cognitive aspects.

Model summary

R	R²	Adjusted R²	Standard Error of the Estimate
0,622[a]	0,387	0,358	0,32499

a. Predictors: (Constant), Bells test total omissions

ANOVA

	Sum of squares	DF	Mean square	F	Sig
Regression	1,400	1	1,400	13,256	0,002[b]
Residual	2,218	21	0,106		
Total	3,618	22			

a. Dependent Variable: Cognitive difficulty reached at the end of all sessions
b. Predictors: (Constant), Bells test total omissions

Coefficients

	Unstandardized Coefficients		Standardized coefficients			Collinearity statistics	
	B	Std Error	Beta	t	Sig	tolerance	VIF
(Constant)	0,840	0,090		9,283	0,000		
Bells test TO	-0,071	0,019	-0,622	-3,641	0,002	1,000	1,000

a. Dependent variable: Cognitive difficulty reached at the end of all sessions

Excluded Variables

	Beta in	T	Sig	Partial correlation	Tolerance	VIF	Minimum Tolerance
Bells test OA	-0,195[b]	-0,876	0,391	-0,192	0,595	1,680	0,595
MAT total omissions	-0,108[b]	-0,483	0,634	-0,107	0,611	1,637	0,611
MAT total MRT	-0,310[b]	-1,697	0,105	-0,355	0,804	1,243	0,804
MAT OA	0,077[b]	0,270	0,790	0,060	0,379	2,636	0,379
MAT MRT OA	0,029[b]	0,161	0,874	0,036	0,918	1,089	0,918
MAT FP asymmetry	0,227[b]	1,258	0,223	0,271	0,869	1,150	0,869

a. Dependent Variable: Cognitive difficulty reached at the end of all sessions
b. Predictors in the Model: (Constant), Bells test total omissions

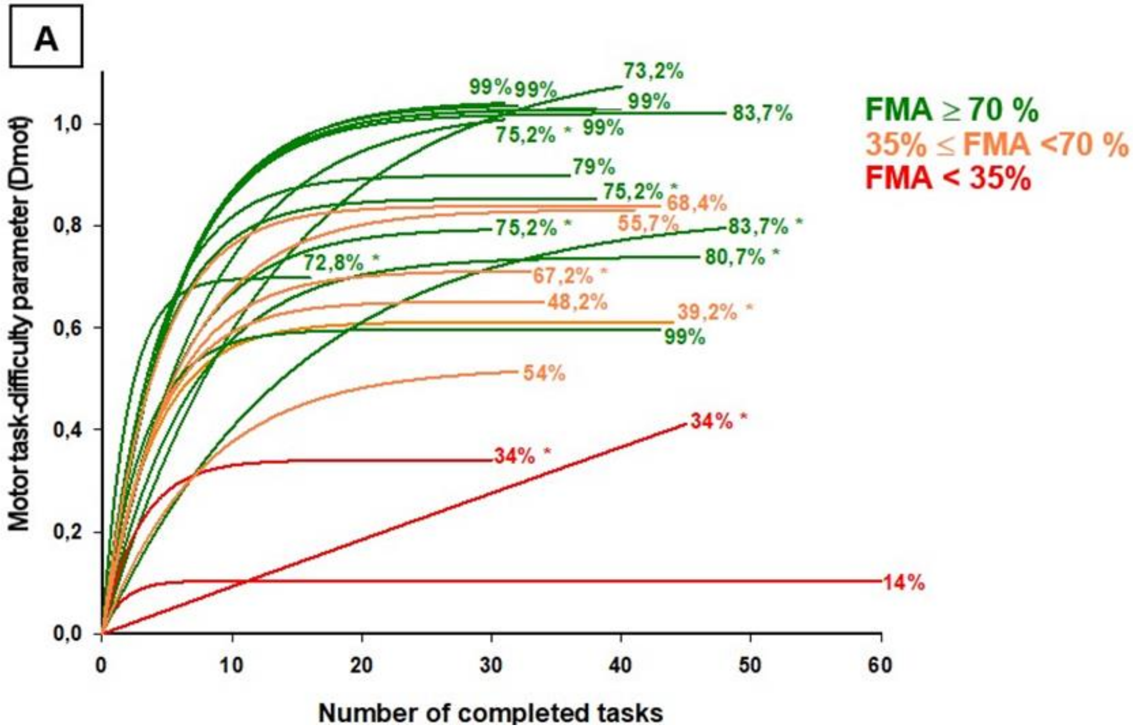
Abbreviations: ANOVA, Analysis of Variance; **DF**, Degrees of Freedom; **Std**, Standard; **Sig**, significance; **VIF**, Variance Inflator Factor; **TO**, total omissions; **OA**, omissions asymmetry; **MAT**, MonAmour Test; **MRT**, Mean Reaction Time; **FP**, False Positive.

The way motor and attentional task-difficulty parameters evolved during three consecutive ROBiGAME sessions were graphically represented for all participants in Figure 3 (graph A for Dmot and graph C for Dcog). As illustrated, participants with a higher FMA-UE score reached a higher level of motor task-difficulty and participants with HSN reached on average lower attentional task-difficulty levels than participants without HSN. Also, in most cases, levels of difficulty progressively increased until a certain level and reached a plateau as illustrated on Figure 3, graphs A and C.

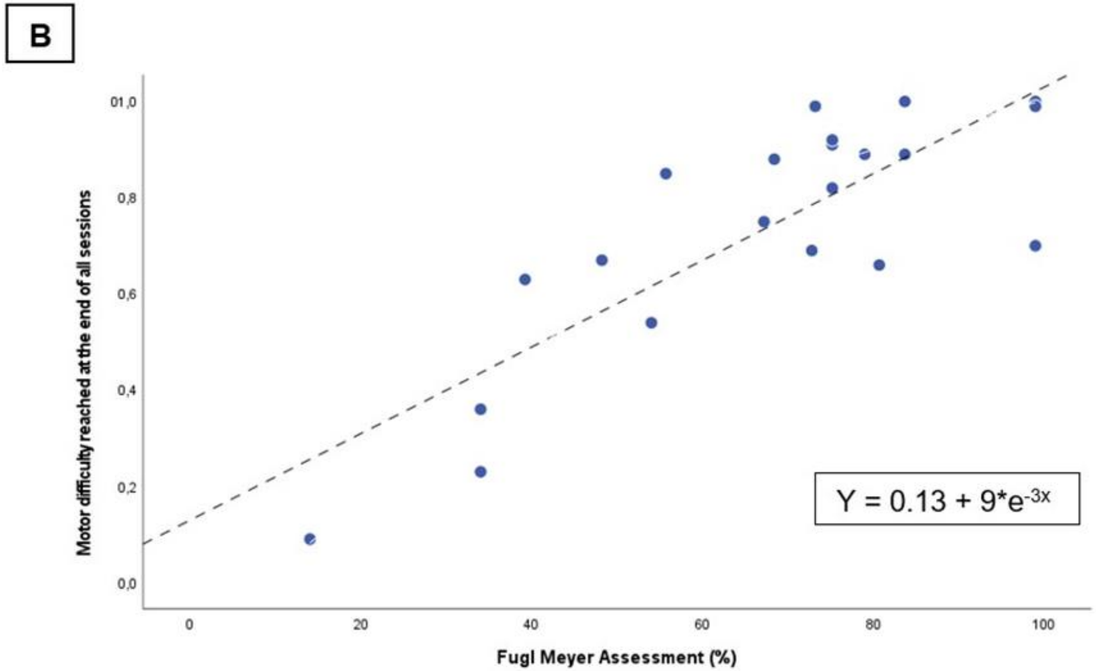
Supplementary Figure 3 constitutes a typical trace of ROBiGAME's DDA mechanism in action. Specifically, it illustrates how motor (Figure S3A for Dmot) and attentional (Figure S3B for Dcog) difficulty evolved over the course of the three sessions for one participant (participant 11). On average, 15 to 20 tasks are performed per session. The dots on the graphs represent the value of the corresponding task-difficulty parameter after the completion of each task. The dotted line in each graph corresponds to the average value of the task-difficulty parameter for the last 10 performed tasks. As shown in these graphs, beyond completion of approximately 15 to 20 tasks, task-difficulty parameters dynamically fluctuate around an individualized plateau value.

A repeated measures ANOVA showed no significant differences between levels of motor task-difficulty reached after completion of the first 20 tasks and mean value of motor task-difficulty reached at the end of all sessions (mean of the last 10 performed tasks). This confirms that individualized levels of task-difficulty were reached after approximately thirty minutes of training, corresponding to completion of 15 to 20 tasks, which indicates a rapid adjustment of task-difficulty to each participants' individual degree of impairment. Finally, the mean success rate of participants was of 76% in all sessions.

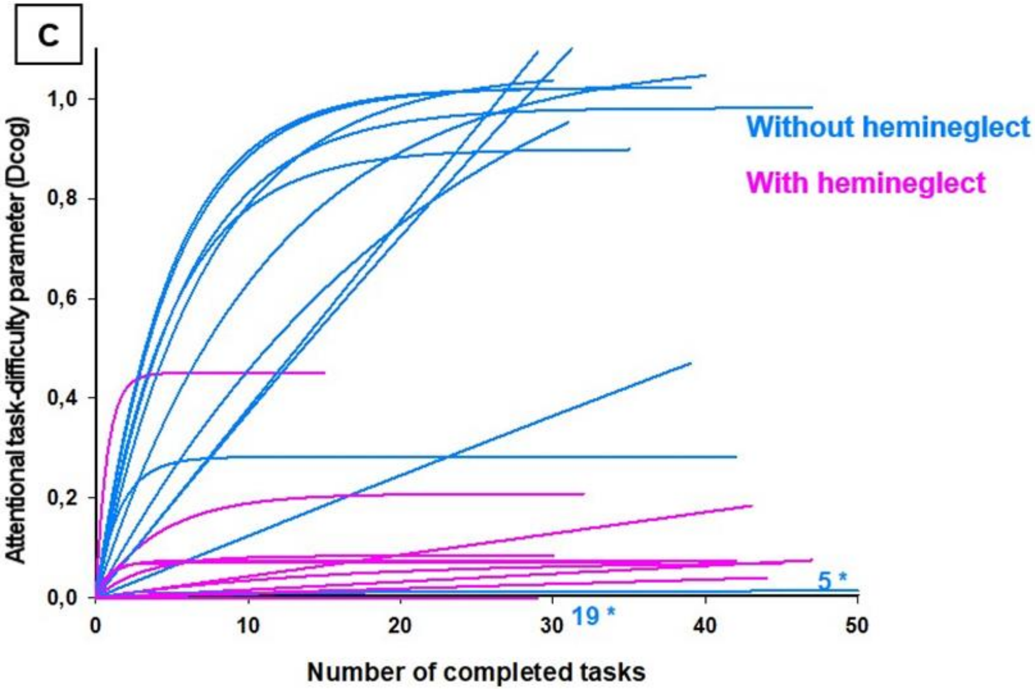
Figure 3. Evolution of game difficulty parameters and relationship with functional assessment scores



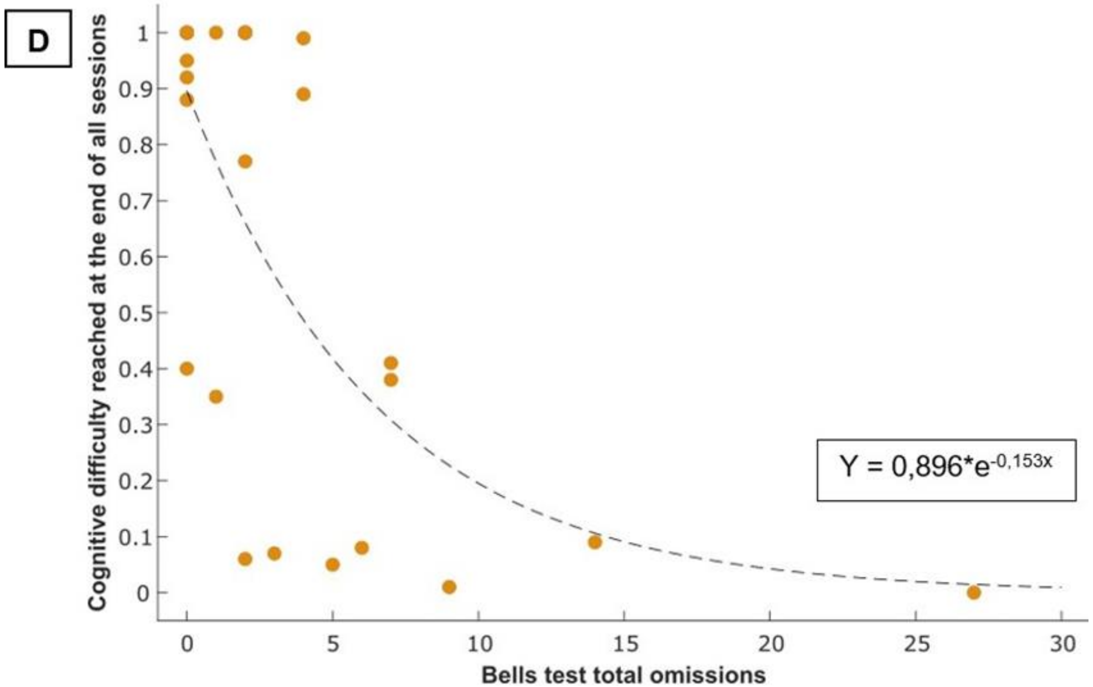
A: Evolution of motor task-difficulty parameters (Dmot) during three ROBiGAME sessions. Each line represents one participant. Participants with hemispatial neglect are annotated with an asterisk (*) symbol.



B: Relationship between FMA-UE with respective motor difficulty scores reached at the end of three ROBiGAME sessions. General tendency of data is illustrated through dotted function and equation.



C: Evolution of attentional task-difficulty parameters (Dcog) during three ROBiGAME sessions. Each line represents one participant (participants numbers' 5 and 19 are annotated to improve readability).



D: Relationship between Bells Test total omissions score with respective attentional difficulty scores reached at the end of three ROBiGAME sessions. General tendency of data is illustrated through dotted function and equation.

Figure S3A. Evolution of motor task-difficulty (Dmot) during training for participant 11.

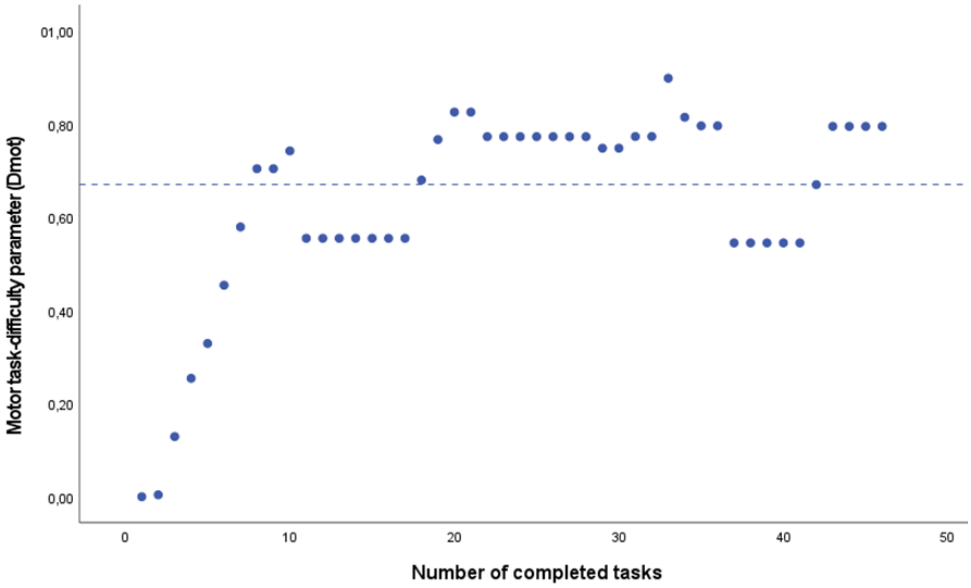
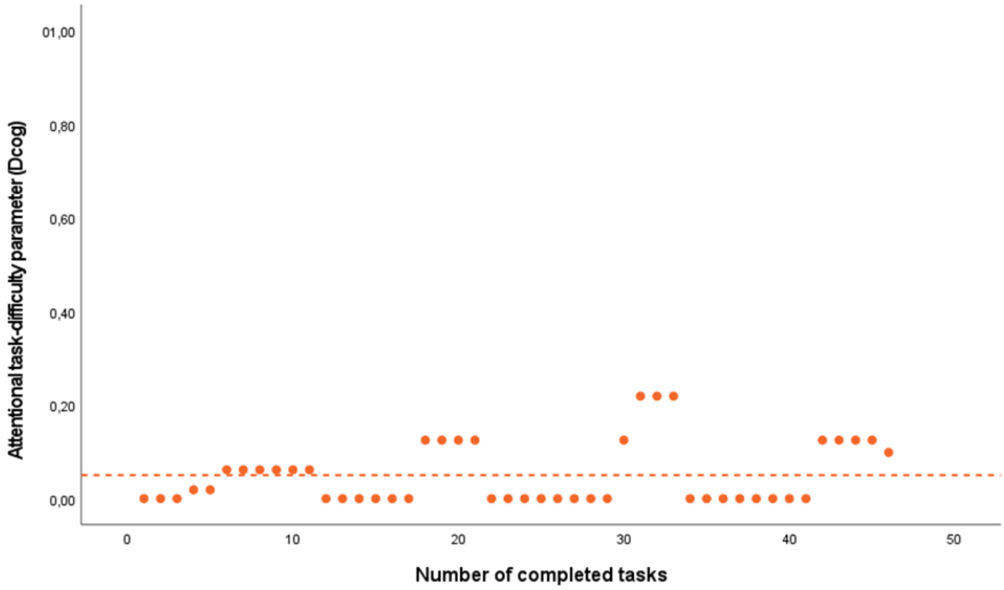


Figure S3B. Evolution of attentional task-difficulty (Dcog) during training for participant 11.



2.5 Discussion

Main findings

This work demonstrated how task-difficulty adequately adapted to match individual degrees of impairment during serious game robotic training for combined rehabilitation of motor and attentional impairments after stroke. Additionally, by studying relationships between functional evaluation scores of both motor and attentional impairments and respective task-difficulty parameters, we suggest a novel way to perform clinical validation of a DDA mechanism. Principal component analysis illustrated that overall difficulty regulation of the system was dictated by two subsets of parameters, one subset concerning motor impairments and the other subset concerning attentional impairments. Our findings recommend that adaptation of parameters determining motor and attentional task-difficulty can be adequately performed simultaneously, allowing combined rehabilitation with individualized levels of difficulty.

Task-difficulty adjustment mechanisms during RAT and serious games: a common validation methodology?

Patients after stroke present various profiles in terms of types and severity of impairments, activity limitations and recovery trajectories [100]. Consequently, their rehabilitation and functional objectives vary widely, evolve over time and thus should be assessed individually and dynamically. In robotic and gamified rehabilitation, various ways to appropriately adjust task-difficulty during training have been described in scientific literature [43, 52, 78, 81]. A strategy for task-difficulty selection is to perform adaptation manually through direct therapist intervention, using the Wizard-of-Oz paradigm [43, 79]. However, when using this method, the selection of task-difficulty relies on subjective assessment and necessitates validation via an experienced therapist, who is usually physically present before or during training. Other adaptive mechanisms were configured, using objective data-driven approaches, to automatically adjust task-difficulty during training and optimize therapists' time [78]. For example, task-difficulty adaptation can be performed according to heuristic parameter increments based on pre-assessment [93] or using partially observable Markov decision process models [101].

Following their development, automated mechanisms should undergo validation in order to confirm that task-difficulty adaptation is performed adequately by the system and corresponds to the patient' rehabilitation needs. Indeed, the way task-difficulty is initially selected and then adapted during therapy is important because this choice could influence efficacy of the intervention, and most importantly performance and motivation of the participants during treatment [102]. Interestingly, serious games using a DDA mechanism, like the one developed by our team for ROBiGAME, seem to offer various benefits compared to random, incremental or no difficulty regulation [52]. It is suggested that serious games using DDA mechanisms lead to a higher number of completed tasks per session, an optimal success rate in total number of completed tasks and a better modulation of training induced fatigability and motivation [52, 81]. Consequently, having the possibility to rapidly offer RAT or serious games with individualized difficulty, adjustable in real-time, could presumably outperform fixed difficulty algorithms in motor learning [103]. Additionally, based on our findings, task difficulty during RAT could be set to the appropriate level of difficulty at the beginning of training, according to the patients' functional assessment scores.

To the best of our knowledge, there is a lack of consensus in scientific literature on a validation methodology for automated mechanisms adjusting task-difficulty, during RAT or serious games training. This may be due to the underlying complexity of defining a common validation methodology for various types of previously described mechanisms. Previous works in literature have described different ways to perform validation of such mechanisms aiming to balance exercise difficulty during training [93, 101, 103]. For example, performance of the system could be validated according to a human therapist's agreement to the decisions made by the system [101]. Other studies conducted validation through participants' perceived performance to different levels of difficulty, through questionnaires [52]. However, these methods rely on an individual expert's judgement or patient-reported measures and hence present limitations. Other described ways to perform validation is to study how changes in difficulty conditions (easy, balanced, hard) lead to differences in the number of successful trials and other performance metrics (i.e., more successful trials and better performance metrics for easier difficulty levels and vice versa for harder difficulty levels) [44]. Although a data-driven assessment is included in this method, the individual patient's degree of impairment is not taken into direct consideration. Finally, it has been suggested that studying the relationship between difficulty level progression and functional impairment scales constitutes a way to evaluate whether difficulty adaptation is optimally performed during RAT [93]. Our study puts this validation approach into implementation and encourages further integration of functional evaluations, using clinical and robotic tests, when performing validation of DDA mechanisms.

Challenges for DDA during combined motor and cognitive rehabilitation after stroke

A meta-analysis focusing on tasks performed in virtual environments after stroke suggested that combined training approaches may lead to better recovery outcomes, especially regarding motor function and activities of daily living [42]. Another recent study has suggested that combining cognitive exercises to motor rehabilitation using RAT could lead to improvements in cognitive impairments beyond motor function [45]. Data made available through serious games, implemented on robotic devices, could help differentiate profiles and thus target specific cognitive improvements in addition to motor recovery [26]. In line with literature, our work showcases that incorporating cognitive exercises into motor tasks on a robotic device could allow simultaneous training, with individualized levels of difficulty.

Based on our results, motor task-difficulty ($R^2 = 0.710$; $p<0.05$) appears to be mainly influenced by the severity of the motor impairment. On the other hand, attentional task-difficulty ($R^2 = 0.387$; $p<0.05$) seems to be affected by additional factors, other than simply the presence or absence of HSN. This may be due to concurrent presence in our sample of cognitive impairments beyond HSN or broader attentional deficits, such as executive or memory impairments. Additionally, contrary to motor evaluation tests, the clinical and robotic evaluation tests used in our work for HSN are simple binary classifiers, meaning they allow to detect the presence or confirm the absence of HSN [65, 88]. This means that, these tests do not allow an established classification concerning the severity of attentional impairment. This could also explain the attribution of similar attentional task-difficulty by the system in some cases where impairment severity seems to be different, as illustrated in Figures 3C&D. A recent scoping review highlighted the lack of robotic assessment tools for categorisation of HSN, based on subtypes and degrees of severity [9]. It is therefore indicated that there is a contrast in terms of precision and standardisation of tools when comparing evaluation of motor and cognitive functions. Consequently, this may explain why our results suggest a more straightforward task-difficulty adaptation for motor impairments and a more challenging one for attentional impairments.

Finally, standardized evaluation for motor impairments is performed at specific time points after stroke (day 7, 6 weeks, 3 months, 6 months, etc) [89], not on a daily or weekly basis. Task-difficulty parameters defined during RAT, such as those described in the present study, could complement existing methods to assess patients and track recovery using regular time points. Being easily accessible, in real time during training, acquisition of such parameters would not require therapists to dedicate additional effort.

Strengths and limitations

Using a novel approach, this proof of concept demonstrated ROBiGAME's ability to adapt task-difficulty to varying levels of impairment after stroke. Previous studies have showed how difficulty adapted to patients that presented with motor impairments of moderate severity [93, 101, 102]. This clinical validation was performed on a sample presenting a wide spectrum of types of impairments (motor and/or attentional) and severity (mild, moderate, severe). Moreover, heterogeneity of our sample indicates that ROBiGAME has an intuitive interface and is appropriate for use with a large population of patients after stroke.

In addition to clinical functional scales, we performed evaluation using quantitative data, acquired through the robotic device, of both motor and attentional impairments. However, cognitive evaluation of participants focused on HSN since ROBiGAME was specifically developed to address this impairment. Therefore, evaluation of other types of cognition which could additionally influence performance during training, such as executive functions or memory, was not conducted. Also, sensory deficits were not thoroughly evaluated. Measures regarding motivational aspects or patient enjoyability, which could impact long term adherence, were also not evaluated in this work.

Finally, the DDA mechanism, validated in this study, is not bound to ROBiGAME and could potentially be implemented on other devices or other serious games, broadening potential applicability.

Areas for future study

Recovery after stroke is usually a long process and future investigations should track evolution of task-difficulty parameters over longer periods of time than three consecutive days of training, as described in this proof of concept. This could help determine the added value of additional evaluation time points in comparison to current guidelines (7 days, 6 weeks, 3 months, 6 months) regarding prognostic prediction models and recovery trajectories [104]. In addition to functional outcomes and task-difficulty parameters, motivation during sessions should be further assessed. Some serious games use reward systems, such as the collection of points during the game scenario, modulating motivation [81]. Whether motivation in stroke recovery is influenced by modulation of task-difficulty over time or reward systems during gameplay should be further studied [105]. Additionally, future trials should investigate whether systems using a DDA mechanism like the one described in our work could lead to better rehabilitation outcomes compared to non-adaptive approaches.

Finally, validation of ROBiGAME's DDA mechanism opens perspectives in terms of self- and tele- evaluation and home rehabilitation. Indeed, after a period of initial guided training and familiarization, evaluation and serious game training could be performed autonomously, with no or distant supervision. Accustomed participants could receive extrinsic feedback between sessions to autonomously track their progress on a more regular basis. In the era of personalized medicine, these data collected through serious games, such as task-difficulty parameters described in ROBiGAME, could feed existing prediction models. ARAT or SAFE score are already available on the internet for prediction models concerning motor impairments [104]. Future models could further include other parameters for prediction of recovery regarding cognitive impairments.

2.6 Conclusions

This proof of concept clinically validated a DDA mechanism for RAT after stroke. ROBiGAME provides simultaneous motor and cognitive exercises with task-difficulty parameters strongly related with respective clinical and robotic evaluation scores. Thus, tasks performed during training were individualized to each participant's impairments, suggesting an optimal level of challenge which could enhance rehabilitation efficacy and help achieve functional goals. Also, an individualized level of game difficulty matching the participants' degree of impairment was rapidly reached after only one RAT session (approximately thirty minutes). This rapid adjustment of the system ensures efficiency and facilitates implementation in clinical practice.

CHAPTER III – Serious games for UL rehabilitation after stroke: a meta-analysis

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Published in Journal of Neuroengineering & Rehabilitation 2021;18(1):100.

doi:10.1186/s12984-021-00889-1

3.1 Abstract

Background: Approximately two thirds of stroke survivors maintain UL impairments and few among them attain complete UL recovery six months after stroke. Technological progress and gamification of interventions aim for better outcomes and constitute opportunities in self- and tele-rehabilitation.

Objectives: Our objective was to assess the efficacy of interventions using serious games, implemented on different types of technological systems, targeting UL rehabilitation after stroke. In addition, we investigated whether adherence to neurorehabilitation principles influenced efficacy of interventions.

Method: This systematic review was conducted according to PRISMA guidelines (PROSPERO registration number: 156589). Two independent reviewers searched PubMed, EMBASE, SCOPUS and Cochrane Central Register of Controlled Trials for eligible randomized controlled trials (PEDro score ≥5). Meta-analysis, using a random effects model, was performed to compare effects of interventions using serious games, to conventional treatment, for UL rehabilitation in adult stroke patients. In addition, we conducted subgroup analysis, according to adherence of included studies to a consolidated set of 11 neurorehabilitation principles.

Results: Meta-analysis of 42 trials, including 1760 participants, showed better improvements in favour of interventions using serious games when compared to conventional therapies, regarding UL function (SMD = 0,47; 95% CI = 0,24 to 0,70; P < 0.0001), activity (SMD = 0,25; 95% CI = 0,05 to 0,46; P = 0.02) and participation (SMD = 0,66; 95% CI = 0,29 to 1,03; P = 0.0005). Additionally, long term effect retention was observed for UL function (SMD = 0,42; 95% CI = 0,05 to 0,79; P = 0.03). Interventions using serious games that complied with at least 8 neurorehabilitation principles showed better overall effects. Although heterogeneity levels remained moderate, results were little affected by changes in methods or outliers indicating robustness.

Conclusion: This meta-analysis showed that interventions in form of serious games, targeting UL rehabilitation after stroke, lead to better improvements, compared to conventional treatment, in three ICF-WHO components. Higher adherence to a consolidated set of neurorehabilitation principles enhance efficacy of interventions implemented on different types of technological systems. Future development of stroke-specific rehabilitation interventions should further take into consideration the consolidated set of neurorehabilitation principles.

Keywords: stroke, upper extremity, serious games, virtual reality, robotics

3.2 Background

Each year more than 1 million Europeans suffer from stroke and approximately two-thirds of survivors maintain UL paresis [8]. This number is expected to rise by 35% in upcoming years [106] leading to additional rehabilitation needs. To this date, few people attain complete UL recovery 6 months after stroke [107]. New interventions targeting the UL aim for better outcomes in ADL, functional independence and quality of life. Alongside conventional therapies, recent developments offer possibilities in self- and tele-rehabilitation [108] which could help manage, cost-efficiently [109], increasing rehabilitation demands.

Technological improvements in RAT and VRS enhance patient care and facilitate therapist assistance during UL rehabilitation [25, 110]. First, RAT promotes the use of the affected limb, intensifies rehabilitation through task repetition and offers task-specific practice [110]. Effectiveness of RAT is established for UL rehabilitation after stroke [36, 38]. Secondly, VRS provide augmented feedback, preserve motivation and are becoming cost-efficient [109]. Recent meta-analyses suggest a superior effect of VR-based interventions compared to conventional treatment on UL function and activity after stroke, especially if developed for this specific purpose [42, 61, 111]. Authors attributed these findings to the fact that VRS specifically developed for rehabilitation, as opposed to commercial video-games, fulfil numerous neurorehabilitation principles.

Typically, a common denominator of VRS and RAT is playful interventions by means of serious games [75, 112]. A serious game is defined as a game that has education or rehabilitation as primary goal. These games combine entertainment, attentional engagement and problem solving to challenge function and performance [52, 62]. Moreover, they comply with several motor relearning principles that constitute the basis of effective interventions in neurorehabilitation [61, 62]. For example, some devices adapt game difficulty to stimulate recovery and maintain motivation [52].

Others incorporate functional tasks mimicking ADL in virtual environments and provide performance feedback during and/or after task completion [113]. Characteristics of serious games differ depending on targeted rehabilitation purposes and technical specificities of the system they are implemented on.

Previous work on the efficacy of VR-based interventions indicated that serious games may enhance UL recovery after stroke [42, 59, 61]. However, why such interventions, specifically developed for rehabilitation purposes and implemented on various types of devices (such as robots, smartphones, tablets, motion capture systems, etc.), may constitute effective therapies for UL rehabilitation after stroke needs to be further investigated. Recent theoretical research proposed consolidation of commonly acknowledged neurorehabilitation principles [62]. Usually, serious games comply with several of these principles which creates an opportunity to evaluate clinical applicability of the consolidated set of principles. To this day, it remains unclear whether higher adherence to this consolidated set of neurorehabilitation principles enhances efficacy of interventions. In addition, it is not well known whether adherence to specific principles influences efficacy. Finally, rehabilitation effects on participation outcomes remain relatively unexplored. In this context, efficacy of interventions should be addressed in terms of all components of the ICF-WHO model [7].

The main objective of this systematic review and meta-analysis was to address the following question in PICOS form: in adults after stroke (P), do serious games, implemented on various technological systems (I), show better efficacy than conventional treatment (C), to rehabilitate UL function and activity, and patient's participation (O)? A secondary objective was to assess whether higher adherence to a consolidated set of neurorehabilitation principles enhances efficacy of games specifically designed for rehabilitation, irrespective of the technological device used.

3.3 Methods

Design

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [114]. The protocol was registered in International Prospective Register of Systematic Reviews (PROSPERO 2020, registration number: 156589).

Identification and Study Selection

A search strategy looking for relevant literature was developed for PubMed and adapted for the other databases, namely Scopus, Embase and Cochrane Library (Additional file 1). Authors received help from a professional librarian to set up the search strategy. Two investigators (GE and ID) independently retrieved studies. All references were stored in reference management software EndNote X9. After removal of duplicates, remaining references were first screened based on titles and abstracts.

Study eligibility was assessed according to the following criteria: (a) design of randomized controlled trials (RCT) (b) participants were adults undergoing stroke rehabilitation (c) the intervention consisted of games developed for neurorehabilitation purposes and implemented in the following technological devices: robotic systems, VRS, tablets, smartphones and motion capture systems (d) relevant outcomes were employed to assess UL function, UL activity and participation (e) studies were published in French or English before May 5th, 2020. All studies using additional therapeutic modalities such as brain stimulation, electrical stimulation or invasive treatments were excluded.

Systematic reviews assessing effectiveness of VR-based rehabilitation and RAT in stroke recovery were also hand-searched looking for relevant references. Finally, a selection based on full-text was conducted by the same two reviewers. Disagreements were resolved through discussion.

Quality and Risk of Bias Assessment

The PEDro checklist was used for methodological quality assessment of trials [115]. In addition, the Cochrane Collaboration's Risk of Bias tool was employed to conduct a critical appraisal of each trial's internal validity [116].

Data Extraction

The following data concerning patients, interventions, control groups and outcomes were extracted from each study: number of patients enrolled in each group, mean time since stroke, corresponding stroke stage classification (subacute: 7 days to 6 months after stroke, chronic: more than 6 months after stroke) [87], dosage and duration of the intervention, technological device used, type and duration of treatment for the control group, presence of a follow-up assessment and outcomes assessed in each timepoint evaluation. Studies were also assessed in terms of the number of neurorehabilitation principles their intervention fulfilled as described in the review of Maier et al. [61]. These authors described a total of 11 principles presented in Table 1. The two reviewers, independently, investigated whether interventions of included studies fulfilled each one of the neurorehabilitation principles. For each clearly identified principle, one point was attributed to the study. In case available information was vague, missing or did not match the neurorehabilitation principle descriptive' (as mentioned in Table 1), no point was accorded. Then, we calculated a total score out of 11 for each included study.

Table 1. List of neurorehabilitation principles with description established by Maier et al. [61]

Neurorehabilitation principle	**Description**	**Fulfilled in studies (%)**		
		All studies	+	=
Massed practice	Tasks aiming to increase the number of repetitions performed	81	79	85
Dosage	Intensive training: more than a daily session of 60 min on every weekday	52	59	38
Structured practice	Training that includes periods of rest	26	31	15
Task-specific practice	Functional training relevant to ADL	100	100	100
Variable practice	Training that includes different types of tasks	98	97	100
Multisensory stimulation	Training that provides more than two types of sensory feedback	83	90	69
Increasing difficulty	Complexity of tasks changes depending on participants' ability, performance or time	76	76	80
Explicit feedback	Training that provides information about the patient's performance at the end of the task	79	93	46*
Implicit feedback	Training that delivers information about the performance in real time such as visualization of movement or other kinematic properties	74	83	54
Avatar representation	Embodied training by representation of a human or body part	38	41	31
Use of the paretic limb	Promoting the use of the paretic limb	76	76	80

All studies, 42 included in meta-analysis

+, studies with SMD in favour of the experimental group for main outcomes regarding upper limb function

=, studies with SMD in favour of the control group for main outcomes regarding upper limb function

***Statistically significant difference ($p < 0.05$) in Fischer's exact test**

Outcome Measurements

Outcome measures were selected in accordance to the ICF-WHO model [7]. In each category, assessment scales were chosen based on recent literature recommendations [89, 117]. The FMA [118] was used for the body function domain. The ARAT [119], the Box and Block Test (BBT) [120] and the Wolf Motor Function Test (WMFT) [121] were used for the activity domain. The social participation subscale of the Stroke Impact Scale (SIS) [122] was used for the participation domain.

When available, mean improvements in terms of change-from-baseline and their standard deviation (SD) were extracted for each time point. If not available, authors were contacted via email. In case of nonresponse, the mean improvement was calculated through subtraction between post-intervention mean score and pre-intervention mean score. Then, the SD was estimated by using a formula according to the Cochrane Handbook for Systematic Reviews of Interventions [123]. The value of the correlation coefficient was imputed by using data from other studies [113, 124, 125] included in the meta-analysis. Lastly, when only median and quartiles were available, the mean and SD were approximated using the method proposed by Wan et al. [126]. For studies using follow-up evaluations at least one month after the intervention, mean improvements in terms of change-from-baseline were calculated in order to assess long-term effect retention.

Data and Statistical Analysis

Articles scoring below 5/10 on the PEDro scale were excluded due to overall poor methodological quality [127]. In addition, only trials that described conventional therapy used in the comparison group as including occupational, physical or self-therapy were considered for statistical analysis. Statistical analyses were performed using the RevMan 5.3 software [128]. Since different rating scales were used for studied outcomes and results were reported in various ways, standardized mean difference (SMD) and 95% confidence interval (CI) were calculated. This method allowed standardization of results across studies. A random effects meta-analysis model was used for all analyses and statistical significance level was set at $P < 0.05$ [129]. Heterogeneity across trials was estimated using the I^2 test. Heterogeneity was not considered to be significative for a $I^2 < 30\%$ [122].

Subgroup analysis was conducted for RCT whose intervention met at least 8/11 neurorehabilitation principles compared to RCT whose intervention fulfilled less. Another subgroup analysis was performed according to stroke stage, comparing effects of interventions using serious games on subacute and chronic stroke patients. Subgroup analysis were only considered when at least two trials in each subgroup reported a given domain. Furthermore, long-term effect retention for trials that measured outcomes at follow-up was evaluated.

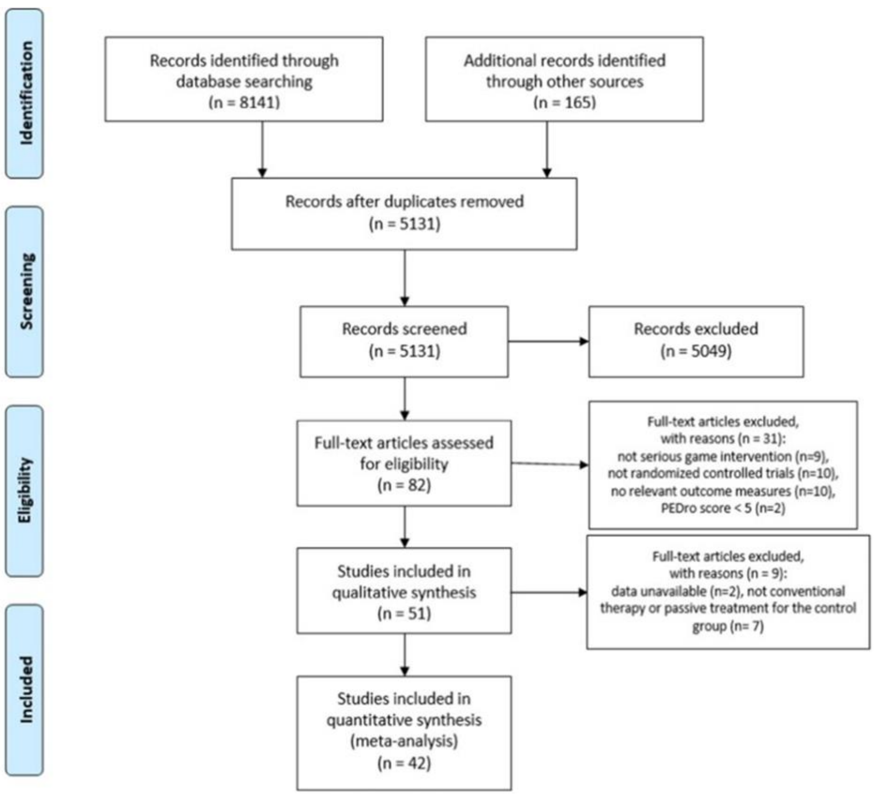
Publication bias was evaluated visually through funnel plot graphic representation. Sensitivity analyses was conducted to verify results robustness in case of funnel plot asymmetry, heterogeneity or presence of outliers. Additional sensitivity analyses were conducted using two different values for correlation coefficient [122]. GRADEpro program was used to assess the strength of the body evidence [130].

3.4 Results

Study Selection

A total of 8141 trials were identified through search across all databases and 165 additional records through other sources. After removal of duplicates, 5131 articles were screened based on titles and abstracts. Among these, 5049 were excluded and 82 full-text articles were assessed for eligibility. 51 RCT were included in the qualitative synthesis. Finally, after quality assessment was performed, 42 RCT were considered for quantitative synthesis. Further details are illustrated in the study PRISMA flow chart (Figure 1).

Figure 1. Flow chart (PRISMA) of the selection process.



Study characteristics

A total of 2083 participants with a mean age ranging from 49.3 to 76.0 years were included in the qualitative synthesis. For each included study, we identified the mean age of the participants, the stroke stage classification and the type of device used for intervention (Table 2). Approximately one third (31%) of studies included stroke patients at subacute stage and two-thirds (69%) at chronic stage. Across trials, serious games were implemented on different types of devices: 26 (51%) used a motion capture system among which many low-cost systems (such as Microsoft Kinect for example), 10 (19%) used an end-effector type robot, 5 (9%) used motion capture gloves, 3 (7%) a robotic exoskeleton, 3 (6%) an immersive-VR system, 2 (4%) a smartphone or tablet, 1 (2%) a surface EMG-controlled sensor and 1 (2%) an arm support system

Table 2. Characteristics of included studies

Author	Participants[a]	Age[b]	Stroke stage	Type of device	PEDro score
Adomaviciene 2019	42	64.6	Subacute	Motion capture system, LCD monitor	5
Ang 2014	21	54.2	Chronic	Haptic Knob robotic system, LCD monitor	6
Aprile 2020	224	69.5	Subacute	4 different robotic devices	6
Askin 2018	38	55.0	Chronic	Motion capture system, LCD monitor	6
Brunner 2017	120	62.0	Subacute	Motion capture gloves, LCD monitor	7
Cameirao 2011	19	61.0	Subacute	Motion capture system, data gloves, LCD monitor	5
Cameirao 2012	44	62.0	Chronic	Motion capture system, data gloves, LCD monitor	6
Cho 2019	38	60.0	Chronic	End-effector robot, LCD monitor	8
Choi 2016	24	61.0	Subacute	Smartphone and tablet computer	6
Crosbie 2012	18	60.0	Chronic	Immersive VR motion tracking system	8
Dehem 2019	45	67.3	Subacute	End-effector robot, LCD monitor	7
Duff 2012	21	68.5	Chronic	Motion capture system, LCD monitor	5
Henrique 2019	31	76.0	Chronic	Immersive VR motion tracking system	5
Housman 2009	28	55.0	Chronic	Robotic exoskeleton, LCD monitor	5
Hung 2019	33	58.5	Chronic	Motion capture system, LCD monitor	7
Jang 2005	10	57.1	Chronic	Motion capture system, LCD monitor	5
Jo 2012	29	64.0	Chronic	Motion capture system, LCD monitor	5
Kim 2018	23	53.5	Subacute	Motion capture system, LCD monitor	8
Kiper 2011	80	64.0	Subacute	Motion capture system, LCD monitor	5

Kiper 2014	44	64.3	Subacute	Motion capture system, LCD monitor	5
Kiper 2018	136	63.9	Subacute	Motion capture system, LCD monitor	6
Klamroth-Marganska 2014	73	56.5	Chronic	Robotic exoskeleton, LCD monitor	8
Kottink 2014	18	61.5	Chronic	Motion capture system, LCD monitor	6
Kwon 2012	26	57.5	Subacute	Motion capture system, LCD monitor	5
Laffont 2019	51	58.0	Subacute	Touchscreen interface, computer monitor	8
Lee 2016 (a)	26	67.5	Chronic	Motion capture system, LCD monitor	8
Lee 2016 (b)	18	71.1	Chronic	Motion capture system, LCD monitor	6
Lee 2018	30	51.0	Chronic	End-effector robot, LCD monitor	6
Levin 2012	12	58.5	Chronic	Motion capture system, LCD monitor	6
Liao 2012	20	54.5	Chronic	End-effector robot, LCD monitor	7
Mugler 2019	32	58.0	Chronic	Surface EMG-controlled sensor, computer monitor	6
Nijenhuis 2016	19	60.0	Chronic	Arm support system	6
Norouzi-Gheidari 2019	18	49.9	Chronic	Motion capture system, LCD monitor	7
Ogun 2019	65	60.6	Chronic	Immersive VR motion tracking system	6
Oh 2019	31	55.0	Chronic	3-D manipulator, computer monitor	7
Park 2019	25	52.5	Chronic	2-D planar motion handlebar, LCD monitor	7
Piron 2009	36	65.2	Chronic	Motion capture camera, computer monitor	7
Piron 2010	47	60.5	Chronic	Motion capture system, LCD monitor	8
Prange 2015	68	59.1	Subacute	Arm support system, computer monitor	7

Rogers 2019	21	64.4	Subacute	Touchscreen mega-tablet	6
Schuster-Amft 2018	54	61.3	Chronic	Motion capture gloves, LCD monitor	8
Shin 2014	16	49.3	Subacute	Motion capture system, LCD monitor	5
Shin 2015	32	54.0	Chronic	Motion capture system, LCD monitor	6
Shin 2016	46	58.5	Chronic	Motion capture gloves, LCD monitor	7
Subramanian 2012	32	61.0	Chronic	Motion capture system, LCD monitor	7
Thielbar 2014	14	56.5	Chronic	Pneumatically actuated motion capture gloves	6
Thielbar 2019	20	59.7	Chronic	Motion capture system, LCD monitor	5
Tomic 2017	26	57.4	Subacute	End-effector robot, LCD monitor	7
Wolf 2015	99	56.9	Chronic	End-effector robot, computer touch screen	7
Yin 2014	23	58.3	Subacute	Motion capture system, computer monitor	6
Zondervan 2016	17	59.5	Chronic	Motion capture gloves, computer monitor	6

Abbreviations: LCD monitor, liquid-crystal display monitor; 3-D, 3-Dimensional; 2-D, 2-Dimensional

[a]Participants: number of total participants in study

[b]Age: mean age in years estimated for total number of participants included in each study

Table 3. Duration, matched groups, outcome measurements, overall findings, number of included neurorehabilitation principles

Authors and publication year	Duration[a]	Matched groups[b]	UL function	UL activity	Participation	Overall findings[c]	Principles[d]
Adomaviciene 2019	2	✓	FMA-UE	BBT		+	4
Ang 2014	6	✓	FMA-UE			=	5
Aprile 2020	6	✓	FMA-UE [s]	ARAT [s]		=	10
Askin 2018	4	X	FMA-UE [m, s]	BBT [m, s]		+	6
Brunner 2017	4	✓		ARAT [s], BBT		=	4
Cameirao 2011	12	✓	FMA-UE			+	6
Cameirao 2012	4	✓	FMA-UE	BBT		+	6
Cho 2019	6	✓	FMA-UE	ARAT, BBT		+	6
Choi 2016	2	✓	FMA-UE [s]			+	8
Crosbie 2012	3	✓		ARAT [s]		=	6
Dehem 2019	9	✓	FMA-UE	BBT	SIS	+	9
Duff 2012	4	✓	FMA-UE [m, s]	WMFT [m, s]	SIS	=	9
Henrique 2019	12	✓	FMA-UE			+	9
Housman 2009	9	✓	FMA-UE			+	5
Hung 2019	12	✓	FMA-UE [m, s]	WMFT [m, s]		=	8
Jang 2005	4	✓	FMA [s]	BBT [s]		+	10

Jo 2012	4	X		WMFT		+	9
Kim 2018	2	✓	FMA-UE ^{s}	BBT ^{s}		=	7
Kiper 2011	4	✓	FMA-UE ^{s}			+	9
Kiper 2014	4	✓	FMA-UE ^{s}			+	9
Kiper 2018	4	✓	FMA-UE ^{s}			+	8
Klamroth-Marganska 2014	8	✓	FMA-UE		SIS	+	7
Kottink 2014	6	✓	FMA-UE	ARAT		=	6
Kwon 2012	4	X	FMA-UE ^{s}			=	5
Laffont 2019	6	✓	FMA-UE	BBT, WMFT		=	8
Lee 2016 (a)	8	✓	FMA-UE ^{s}	BBT ^{s}		+	8
Lee 2016 (b)	6	✓		BBT		+	9
Lee 2018	8	✓	FMA-UE ^{s}			+	8
Levin 2012	3	✓	FMA-UE ^{s}	BBT ^{s}, WMFT		+	9
Liao 2012	4	✓	FMA-UE ^{s}			+	7
Mugler 2019	3	X	FMA-UE			=	8
Nijenhuis 2016	6	✓	FMA-UE $^{m, s}$	ARAT $^{m, s}$, BBT	SIS	=	5
Norouzi-Gheidari 2019	4	X	FMA-UE ^{s}	BBT ^{s}	SIS ^{s}	+	8
Ogun 2019	6	✓	FMA-UE ^{s}	ARAT ^{s}		+	8
Oh 2019	6	✓	FMA-UE	BBT		+	9

Park 2019	4	✓	FMA-UE	WMFT	SIS	=	9
Piron 2009	4	✓	FMA-UE [s]			+	8
Piron 2010	4	✓	FMA-UE [s]			+	10
Prange 2015	6	✓		BBT		+	9
Rogers 2019	4	X	FMA-UE [s]			=	5
Schuster-Amft 2018	4	✓		BBT [m, s]	SIS	=	7
Shin 2014	2	X	FMA-UE [s]			=	8
Shin 2015	4	✓	FMA-UE [m, s]			=	9
Shin 2016	4	✓	FMA-UE [s]		SIS [s]	+	10
Subramanian 2012	4	✓	FMA-UE			+	8
Thielbar 2014	6	✓	FMA-UE [s]	ARAT [s]		+	10
Thielbar 2019	4	✓	FMA-UE			+	8
Tomic 2017	3	✓	FMA-UE	WMFT		+	8
Wolf 2015	8	✓	FMA-UE [s]	ARAT [s], WMFT		=	6
Yin 2014	2	✓	FMA-UE [m, s]	ARAT [m, s]		=	11
Zondervan 2016	3	✓		ARAT, BBT		=	7

Abbreviations: UL, UL; FMA-UE, Fugl-Meyer Assessment Upper Extremity subscale; ARAT, Action Research Arm Test; BBT, Box and Block Test; WMFT, Wolf-Motor Function Test; SIS, Stroke Impact Scale; ✓, matched time between interventions; X, time between interventions not matched; +, statistically significant improvement in favour of experimental group for main outcomes; =, no statistically significant differences reported between experimental and control group

[a]Duration: total number of treatment weeks

[b]Matched groups: matched time in terms of daily session time, sessions per week and total number of weeks between experimental and control group.

[c]Overall findings: reported findings concerning primary outcome measures.

[d]Principles: total number of neuro-rehabilitation principles fulfilled by the serious game used in the intervention. A total of 11 principles were examined for each trial.

[m]Studies that reported only median and quartiles; [s]Studies for which the Standard Deviation had to be estimated

For each trial, total treatment duration in terms of minutes per session, number of sessions per week and total number of weeks was identified. In addition, whether intervention and control groups were time-matched regarding these characteristics was verified (Table 3). Total number of weeks of treatment varied from 2 to 12 weeks with a mean of 5 weeks among trials. Daily duration of therapy varied widely among studies ranging from 30 to 225 min. In most trials (85%), total treatment duration was matched between the intervention and control groups (Table 3).

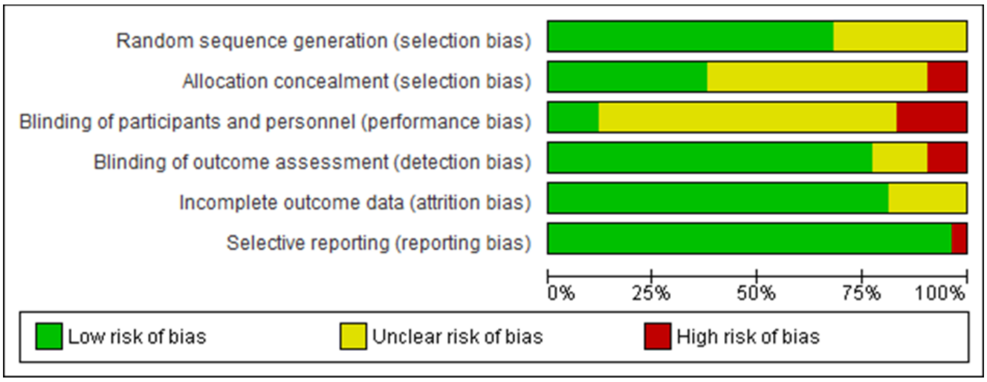
The number of neurorehabilitation principles fulfilled by serious games were identified through content analysis. This number varied from 4 to 11 (Table 3). For a total of 11 neurorehabilitation principles, 32 (63%) interventions met 8 or more, 17 (33%) met between 5 and 7 and 2 (4%) interventions met less than 5. Table 1 illustrates the percentage of studies included in meta-analysis that complied with each neurorehabilitation principle. In addition, Table 1 displays differences in adherence to each neurorehabilitation principle between studies with overall positive or negative results (based on each study SMD in quantitative synthesis results). Statistically significant differences were observed regarding the principle of explicit feedback. Indeed, the group of studies with overall positive results adheres more to this principle than the other group.

Regarding main outcomes, 44 trials (87%) assessed UL motor function, 30 (59%) assessed UL activity and 9 (17%) assessed participation (Table 3). Most trials (60%) reported significantly superior results in at least one ICF-WHO component in favour of interventions using serious games compared to conventional treatment.

Methodological quality and Risk of Bias assessment

PEDro scores of 51 included studies ranged from 5 to 8 with a mean (SD) of 6.33 (1.15) indicating an overall moderate to high methodological quality (Table 2). Detailed PEDro scale scoring for each trial is illustrated in Supplementary Table 1. In addition, the detailed analysis using the Cochrane Collaboration Risk of Bias tool is presented in Additional Figure 1.

Supplementary Figure 1. Detailed analysis using the Cochrane Collaboration Risk of Bias Tool



Supplementary Table 1. Detailed PEDro scale scoring for each study.

STUDY	TOTAL	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11
Adomaviciene 2019	5	1	1	0	1	0	0	0	1	0	1	1
Ang 2014	6	1	1	0	1	0	0	1	1	0	1	1
Aprile 2020	6	1	1	0	1	0	0	1	0	1	1	1
Askin 2018	6	0	1	0	1	0	0	1	1	0	1	1
Brunner 2017	7	1	1	1	1	0	0	1	1	0	1	1
Cameirao 2011	5	1	1	0	1	0	0	1	0	0	1	1
Cameirao 2012	6	1	1	0	1	0	0	1	1	0	1	1
Cho 2019	8	0	1	1	1	0	0	1	1	1	1	1
Choi 2016	6	1	1	0	1	0	0	1	1	0	1	1
Crosbie 2012	8	1	1	1	1	0	0	1	1	1	1	1
Dehem 2019	7	1	1	1	1	0	0	1	0	1	1	1
Duff 2012	5	1	1	0	1	0	0	1	0	0	1	1
Henrique 2019	5	0	1	0	1	0	0	0	1	0	1	1
Housman 2009	5	1	1	0	1	0	0	1	0	0	1	1
Hung 2019	7	1	1	0	1	0	0	1	1	1	1	1
Jang 2005	5	0	1	0	1	0	0	0	1	0	1	1
Jo 2012	5	1	1	0	1	0	0	0	1	0	1	1
Kim 2018	8	0	1	1	1	1	0	1	0	1	1	1
Kiper 2011	5	1	1	0	1	0	0	0	1	0	1	1
Kiper 2014	5	1	1	0	1	0	0	0	1	0	1	1
Kiper 2018	6	1	1	1	1	0	0	0	1	0	1	1
Klamroth-Marganska 2014	8	1	1	1	1	0	0	1	1	1	1	1
Kottink 2014	6	1	1	0	1	0	0	1	1	0	1	1
Kwon 2012	5	1	1	0	1	0	0	1	0	0	1	1
Laffont 2019	8	1	1	1	1	0	0	1	1	1	1	1
Lee 2016 (a)	8	1	1	1	1	0	0	1	1	1	1	1
Lee 2016 (b)	6	1	1	0	1	0	0	1	1	0	1	1
Lee 2018	6	1	1	0	1	0	0	1	1	0	1	1
Levin 2012	6	1	1	0	1	0	0	1	1	0	1	1
Liao 2012	7	1	1	1	1	0	0	1	1	0	1	1
Mugler 2019	6	0	1	0	1	0	0	1	1	0	1	1
Nijenhuis 2016	6	1	1	1	1	0	0	0	1	0	1	1
Norouzi-Gheidari 2019	7	1	1	0	1	0	0	1	1	0	1	1
Ogun 2019	6	1	1	0	1	1	0	1	0	0	1	1
Oh 2019	7	1	1	1	1	0	0	1	1	0	1	1
Park 2019	7	1	1	1	1	0	0	1	1	0	1	1
Piron 2009	7	0	1	1	1	0	0	1	1	0	1	1
Piron 2010	8	1	1	1	1	0	0	1	1	1	1	1
Rogers	6	1	1	1	1	0	0	0	1	0	1	1
Prange 2015	7	1	1	1	1	0	0	1	1	0	1	1
Schuster-Amft 2018	8	1	1	1	1	0	0	1	1	1	1	1
Shin 2014	5	1	1	0	1	0	0	1	1	0	1	0
Shin 2015	6	1	1	0	1	0	0	1	1	0	1	1
Shin 2016	7	1	1	1	1	1	0	1	0	1	1	1
Subramanian 2012	7	0	1	1	1	0	0	1	1	0	1	1
Thielbar 2014	6	0	1	0	1	0	0	1	1	0	1	1
Thielbar 2019	5	0	1	0	1	0	0	0	1	0	1	1
Tomic 2017	7	1	1	0	1	0	0	1	1	1	1	1
Wolf 2015	7	1	1	0	1	0	0	1	1	1	1	1
Yin 2014	6	1	1	1	1	0	0	0	1	0	1	1
Zondervan 2016	6	0	1	0	1	0	0	1	1	0	1	1

Abbreviations: Item 1: Eligibility criteria specified; Item 2: Random allocation; Item 3: Allocation concealment; Item 4: groups similar at baseline; Item 5: blinding of subjects; Item 6: blinding therapists; Item 7: blinding of assessors; Item 8: > 85% measures obtained; Item 9: "intention to treat" analysis; Item 10: between-group statistical comparisons are reported for at least one key outcome; Item 11: point measures and measures of variability for at least one key outcome

Effect of rehabilitation through serious games on UL motor function

In total, rehabilitation using serious games led to significantly better improvements, of moderate effect size, in UL motor function compared to conventional treatment (SMD = 0,47; 95% CI = 0,24 to 0,70; $P < 0.0001$) (Figure 2). Subgroup analysis highlighted differences between results of trials using serious games fulfilling 8 or more neurorehabilitation principles and those that didn't ($P = 0.003$). Indeed, only interventions that met 8 or more principles showed significant impact of moderate effect size on UL motor function (SMD = 0.62; 95% CI = 0.33 to 0.92; $P = 0.0001$). Although total results indicated considerable heterogeneity between studies ($I^2 = 76$ %), analysis using the GRADE approach led to a moderate certainty of evidence (Supplementary Figure 2 illustrates detailed summary of findings).

Additional subgroup analysis was conducted based on the stroke stage of included participants across studies (Figure 3). Results suggest that interventions using serious games were effective in improving UL motor function in both subacute (SMD = 0.35; 95% CI = 0.10 to 0,59; $P = 0.006$) and chronic stage after stroke (SMD = 0.57; 95% CI = 0.19 to 0.95; $P = 0.003$). Differences among subgroups didn't reach statistical significance ($P = 0.33$).

Finally, in order to address heterogeneity, sensitivity analyses were performed in two ways. A first analysis was conducted by excluding outliers identified through funnel plot graphic representation (Supplementary Figure 3). Then, a second analysis was carried out by using a different correlation coefficient value. In both cases, results indicate no significant differences in total estimates when compared to initial findings (Supplementary Figure 4 and 5).

Figure 2. Forest plot of UL motor function as measured by the FMA-UE: studies using a serious game fulfilling ≥ 8 neurorehabilitation principles versus studies using a serious game fulfilling < 8 neurorehabilitation principles.

	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
1.1.1 Number of neurorehabilitation principles > or = 8								
Aprile 2020	8.5	8.0668	91	8.57	8.0222	99	3.7%	-0.01 [-0.29, 0.28]
Choi 2016	19.08	13.39	12	9.67	14.22	12	2.6%	0.66 [-0.17, 1.48]
Dehem 2019	19.5	18.55	15	10.8	19.58	17	2.9%	0.44 [-0.26, 1.15]
Duff 2012	1.48	4.14	11	6.83	4.51	10	2.4%	-1.19 [-2.13, -0.24]
Henrique 2019	14.69	0.67	16	9.07	1.34	15	1.4%	5.22 [3.66, 6.78]
Hung 2019	3.5	8.65	17	3.38	10.89	16	2.9%	0.01 [-0.67, 0.69]
Jang 2005	7	4.33	5	2.4	2.69	5	1.6%	1.15 [-0.25, 2.55]
Kiper 2011	9.8	10.32	40	1.6	10.91	40	3.4%	0.76 [0.31, 1.22]
Kiper 2014	6.8	8.85	23	3.2	10.73	21	3.1%	0.36 [-0.24, 0.96]
Kiper 2018	9.72	10.77	68	3.14	10.9	68	3.6%	0.60 [0.26, 0.95]
Laffont 2019	24.1	14.8	25	17.8	14.6	26	3.2%	0.42 [-0.13, 0.98]
Lee 2016 (a)	7	10.99	13	-0.31	11.51	13	2.7%	0.63 [-0.16, 1.42]
Lee 2018	8.2	6.35	15	2.33	5.08	15	2.8%	0.99 [0.23, 1.76]
Levin 2012	5	7.5	6	1	7.91	6	2.0%	0.48 [-0.68, 1.63]
Norouzi-Gheidari 2019	2.1	11.42	9	-0.2	7.54	9	2.4%	0.23 [-0.70, 1.15]
Ogun 2019	6.91	5.37	33	1.5	5.44	32	3.3%	0.99 [0.47, 1.51]
Oh 2019	1.9	3	17	2.1	2	14	2.9%	-0.07 [-0.78, 0.63]
Park 2019	1.9	2.8	12	2.1	2.7	13	2.7%	-0.07 [-0.86, 0.71]
Piron 2009	5.1	4.9	18	2.2	2.98	18	2.9%	0.70 [0.02, 1.37]
Piron 2010	7.3	6.86	27	2.6	6.13	20	3.1%	0.70 [0.11, 1.30]
Shin 2014	11.7	6.46	9	6.3	7.44	7	2.2%	0.74 [-0.29, 1.77]
Shin 2015	4.63	6.48	16	5.57	10.25	16	2.9%	-0.11 [-0.80, 0.59]
Shin 2016	4.9	1	24	1.4	0.8	22	2.3%	3.78 [2.79, 4.77]
Thielbar 2014	1.7	6.37	7	1.7	6.68	7	2.2%	0.00 [-1.05, 1.05]
Tomic 2017	18	9.4	13	7.5	5.5	13	2.5%	1.32 [0.46, 2.18]
Yin 2014	15.33	16.92	11	13.63	20.01	12	2.6%	0.09 [-0.73, 0.91]
Subtotal (95% CI)			**553**			**546**	**70.5%**	**0.62 [0.33, 0.92]**
Heterogeneity: Tau² = 0.44; Chi² = 125.70, df = 25 (P < 0.00001); I² = 80%								
Test for overall effect: Z = 4.10 (P < 0.0001)								
1.1.2 Number of neurorehabilitation principles < 8								
Ang 2014	7.2	2.3	8	4.9	4.1	7	2.2%	0.66 [-0.39, 1.72]
Askin 2018	2.25	6.3	18	0.5	7.25	20	3.0%	0.25 [-0.39, 0.89]
Cameirao 2011	84.6	18.4	8	66.9	22.9	8	2.2%	0.81 [-0.23, 1.84]
Housman 2009	3.3	2.4	14	2.2	2.6	14	2.8%	0.43 [-0.32, 1.18]
Kim 2018	10.5	8.58	11	12	11.11	8	2.4%	-0.15 [-1.06, 0.76]
Kottink 2014	1.5	2.3	8	2.3	2.8	10	2.4%	-0.29 [-1.23, 0.64]
Kwon 2012	2.61	3.36	13	5.47	7.7	13	2.7%	-0.47 [-1.25, 0.31]
Liao 2012	6.3	5.64	10	1.3	7.92	10	2.4%	0.70 [-0.21, 1.61]
Nijenhuis 2016	0.3	19.02	9	2	16.63	10	2.5%	-0.09 [-0.99, 0.81]
Prange 2015	7.9	8.3	33	10.2	9.6	33	3.4%	-0.25 [-0.74, 0.23]
Wolf 2015	9.3	25.76	47	9.6	24.98	45	3.5%	-0.01 [-0.42, 0.40]
Subtotal (95% CI)			**179**			**178**	**29.5%**	**0.05 [-0.17, 0.27]**
Heterogeneity: Tau² = 0.01; Chi² = 10.73, df = 10 (P = 0.38); I² = 7%								
Test for overall effect: Z = 0.47 (P = 0.64)								
Total (95% CI)			**732**			**724**	**100.0%**	**0.47 [0.24, 0.70]**
Heterogeneity: Tau² = 0.35; Chi² = 148.44, df = 36 (P < 0.00001); I² = 76%								
Test for overall effect: Z = 3.96 (P < 0.0001)								
Test for subgroup differences: Chi² = 9.07, df = 1 (P = 0.003), I² = 89.0%								

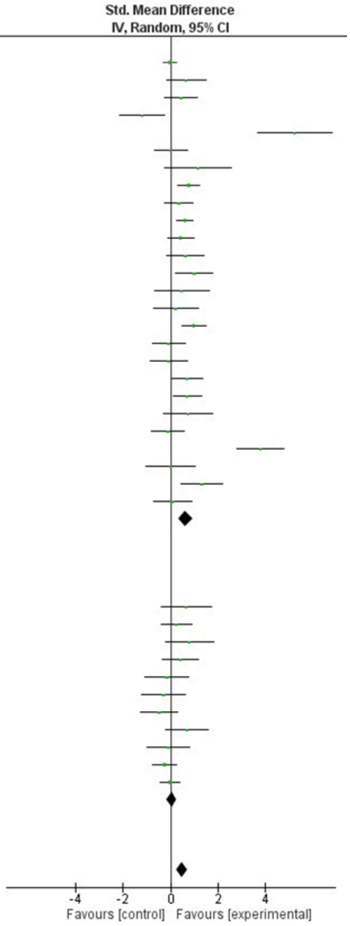


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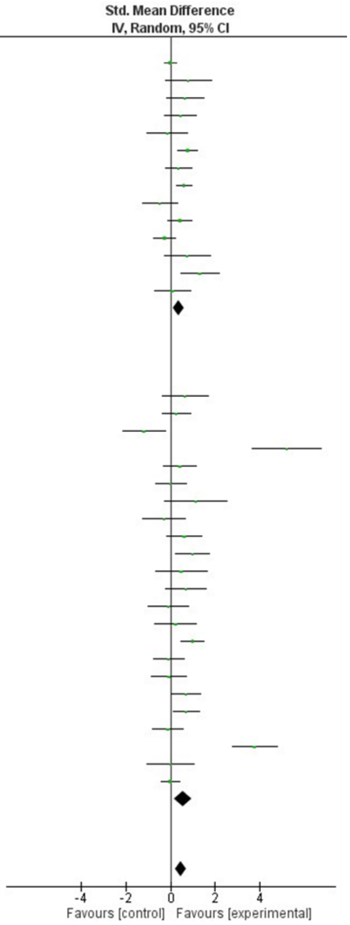
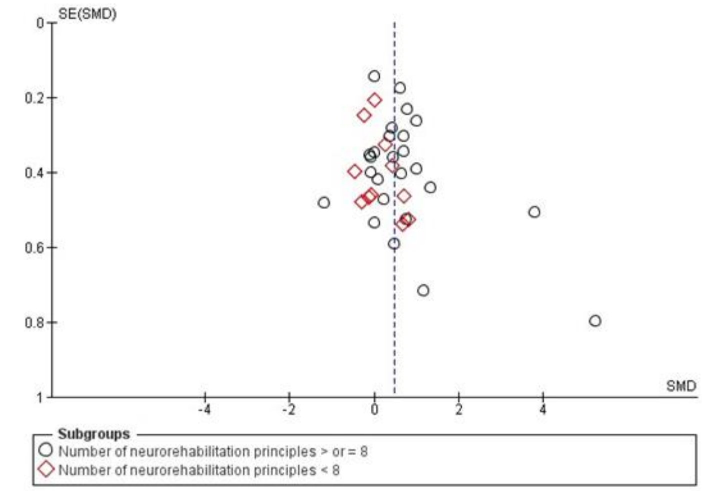
Figure 3. Forest plot of UL motor function as measured by the FMA-UE: studies in the subacute phase after stroke versus studies in the chronic phase after stroke.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.4.1 Subacute								
Aprile 2020	8.5	8.0668	91	8.57	8.0222	99	3.7%	-0.01 [-0.29, 0.28]
Cameirao 2011	84.6	18.4	8	66.9	22.9	8	2.2%	0.81 [-0.23, 1.84]
Choi 2016	19.08	13.39	12	9.67	14.22	12	2.6%	0.66 [-0.17, 1.48]
Dehem 2019	19.5	18.55	15	10.8	19.58	17	2.9%	0.44 [-0.26, 1.15]
Kim 2018	10.5	8.58	11	12	11.11	8	2.4%	-0.15 [-1.06, 0.76]
Kiper 2011	9.8	10.32	40	1.6	10.91	40	3.4%	0.76 [0.31, 1.22]
Kiper 2014	6.8	8.85	23	3.2	10.73	21	3.1%	0.36 [-0.24, 0.96]
Kiper 2018	9.72	10.77	68	3.14	10.9	68	3.6%	0.60 [0.26, 0.95]
Kwon 2012	2.61	3.36	13	5.47	7.7	13	2.7%	-0.47 [-1.25, 0.31]
Laffont 2019	24.1	14.8	25	17.8	14.6	26	3.2%	0.42 [-0.13, 0.98]
Prange 2015	7.9	8.3	33	10.2	9.6	33	3.4%	-0.25 [-0.74, 0.23]
Shin 2014	11.7	6.46	9	6.3	7.44	7	2.2%	0.74 [-0.29, 1.77]
Tomic 2017	18	9.4	13	7.5	5.5	13	2.5%	1.32 [0.46, 2.18]
Yin 2014	15.33	16.92	11	13.63	20.01	12	2.6%	0.09 [-0.73, 0.91]
Subtotal (95% CI)			**372**			**377**	**40.7%**	**0.35 [0.10, 0.59]**
Heterogeneity: Tau² = 0.11; Chi² = 29.53, df = 13 (P = 0.006); I² = 56%								
Test for overall effect: Z = 2.79 (P = 0.005)								
1.4.2 Chronic								
Ang 2014	7.2	2.3	8	4.9	4.1	7	2.2%	0.66 [-0.39, 1.72]
Askin 2018	2.25	6.3	18	0.5	7.25	20	3.0%	0.25 [-0.39, 0.89]
Duff 2012	1.48	4.14	11	6.83	4.51	10	2.4%	-1.19 [-2.13, -0.24]
Henrique 2019	14.69	0.67	16	9.07	1.34	15	1.4%	5.22 [3.66, 6.78]
Housman 2009	3.3	2.4	14	2.2	2.6	14	2.8%	0.43 [-0.32, 1.18]
Hung 2019	3.5	8.65	17	3.38	10.89	16	2.9%	0.01 [-0.67, 0.69]
Jang 2005	7	4.33	5	2.4	2.69	5	1.6%	1.15 [-0.25, 2.55]
Kottink 2014	1.5	2.3	8	2.3	2.8	10	2.4%	-0.29 [-1.23, 0.64]
Lee 2016 (a)	7	10.99	13	-0.31	11.51	13	2.7%	0.63 [-0.16, 1.42]
Lee 2018	8.2	6.35	15	2.33	5.08	15	2.8%	0.99 [0.23, 1.76]
Levin 2012	5	7.5	6	1	7.91	6	2.0%	0.48 [-0.68, 1.63]
Liao 2012	6.3	5.64	10	1.3	7.92	10	2.4%	0.70 [-0.21, 1.61]
Nijenhuis 2016	0.3	19.02	9	2	16.63	10	2.5%	-0.09 [-0.99, 0.81]
Norouzi-Gheidari 2019	2.1	11.42	9	-0.2	7.54	9	2.4%	0.23 [-0.70, 1.15]
Ogun 2019	6.91	5.37	33	1.5	5.44	32	3.3%	0.99 [0.47, 1.51]
Oh 2019	1.9	3	17	2.1	2	14	2.9%	-0.07 [-0.78, 0.63]
Park 2019	1.9	2.8	12	2.1	2.7	13	2.7%	-0.07 [-0.86, 0.71]
Piron 2009	5.1	4.9	18	2.2	2.98	18	2.9%	0.70 [0.02, 1.37]
Piron 2010	7.3	6.86	27	2.6	6.13	20	3.1%	0.70 [0.11, 1.30]
Shin 2015	4.63	6.48	16	5.57	10.25	16	2.9%	-0.11 [-0.80, 0.59]
Shin 2016	4.9	1	24	1.4	0.8	22	2.3%	3.78 [2.79, 4.77]
Thielbar 2014	1.7	6.37	7	1.7	6.68	7	2.2%	0.00 [-1.05, 1.05]
Wolf 2015	9.3	25.76	47	9.6	24.98	45	3.5%	-0.01 [-0.42, 0.40]
Subtotal (95% CI)			**360**			**347**	**59.3%**	**0.57 [0.19, 0.95]**
Heterogeneity: Tau² = 0.66; Chi² = 117.47, df = 22 (P < 0.00001); I² = 81%								
Test for overall effect: Z = 2.96 (P = 0.003)								
Total (95% CI)			**732**			**724**	**100.0%**	**0.47 [0.24, 0.70]**
Heterogeneity: Tau² = 0.35; Chi² = 148.44, df = 36 (P < 0.00001); I² = 76%								
Test for overall effect: Z = 3.96 (P < 0.0001)								
Test for subgroup differences: Chi² = 0.93, df = 1 (P = 0.33), I² = 0%								

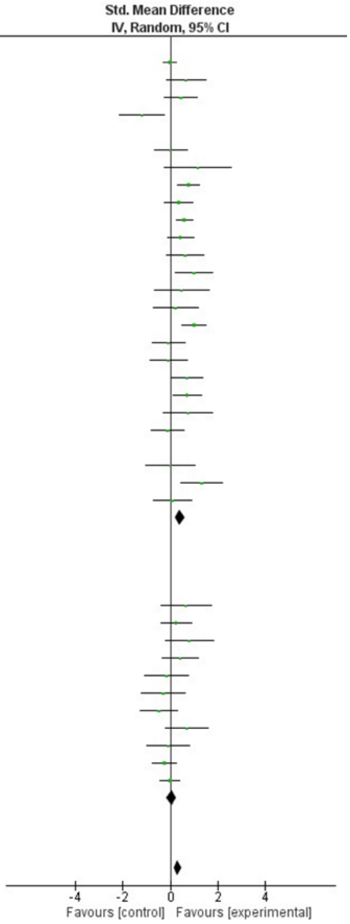


Supplementary Figure 3. Funnel plot graphic representation.



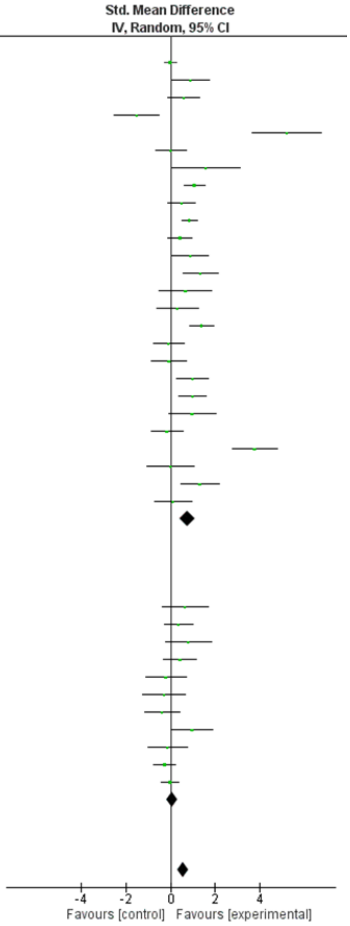
Supplementary Figure 4. Sensitivity analysis without outliers. Forest plot of UL motor function as measured by the FMA-UE: studies using a serious game fulfilling ≥ 8 neurorehabilitation principles versus studies using a serious game fulfilling < 8 neurorehabilitation principles.

	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
1.1.1 Number of neurorehabilitation principles > or = 8								
Aprile 2020	8.5	8.0668	91	8.57	8.0222	99	5.6%	-0.01 [-0.29, 0.28]
Choi 2016	19.08	13.39	12	9.67	14.22	12	2.4%	0.66 [-0.17, 1.48]
Dehem 2019	19.5	18.55	15	10.8	19.58	17	3.0%	0.44 [-0.26, 1.15]
Duff 2012	1.48	4.14	11	6.83	4.51	10	2.0%	-1.19 [-2.13, -0.24]
Henrique 2019	14.69	0.67	16	9.07	1.34	15	0.0%	5.22 [3.66, 6.78]
Hung 2019	3.5	8.65	17	3.38	10.89	16	3.1%	0.01 [-0.67, 0.69]
Jang 2005	7	4.33	5	2.4	2.69	5	1.1%	1.15 [-0.25, 2.55]
Kiper 2011	9.8	10.32	40	1.6	10.91	40	4.4%	0.76 [0.31, 1.22]
Kiper 2014	6.8	8.85	23	3.2	10.73	21	3.5%	0.36 [-0.24, 0.96]
Kiper 2018	9.72	10.77	68	3.14	10.9	68	5.2%	0.60 [0.26, 0.95]
Laffont 2019	24.1	14.8	25	17.8	14.6	26	3.8%	0.42 [-0.13, 0.98]
Lee 2016 (a)	7	10.99	13	-0.31	11.51	13	2.6%	0.63 [-0.16, 1.42]
Lee 2018	8.2	6.35	15	2.33	5.08	15	2.7%	0.99 [0.23, 1.76]
Levin 2012	5	7.5	6	1	7.91	6	1.5%	0.48 [-0.68, 1.63]
Norouzi-Gheidari 2019	2.1	11.42	9	-0.2	7.54	9	2.1%	0.23 [-0.70, 1.15]
Ogun 2019	6.91	5.37	33	1.5	5.44	32	4.0%	0.99 [0.47, 1.51]
Oh 2019	1.9	3	17	2.1	2	14	2.9%	-0.07 [-0.78, 0.63]
Park 2019	1.9	2.8	12	2.1	2.7	13	2.6%	-0.07 [-0.86, 0.71]
Piron 2009	5.1	4.9	18	2.2	2.98	18	3.1%	0.70 [0.02, 1.37]
Piron 2010	7.3	6.86	27	2.6	6.13	20	3.5%	0.70 [0.11, 1.30]
Shin 2014	11.7	6.46	9	6.3	7.44	7	1.8%	0.74 [-0.29, 1.77]
Shin 2015	4.63	6.48	16	5.57	10.25	16	3.0%	-0.11 [-0.80, 0.59]
Shin 2016	4.9	1	24	1.4	0.8	22	0.0%	3.78 [2.79, 4.77]
Thielbar 2014	1.7	6.37	7	1.7	6.68	7	1.7%	0.00 [-1.05, 1.05]
Tomic 2017	18	9.4	13	7.5	5.5	13	2.3%	1.32 [0.46, 2.18]
Yin 2014	15.33	16.92	11	13.63	20.01	12	2.5%	0.09 [-0.73, 0.91]
Subtotal (95% CI)			**513**			**509**	**70.4%**	**0.41 [0.22, 0.61]**
Heterogeneity: Tau² = 0.10; Chi² = 45.97, df = 23 (P = 0.003); I² = 50%								
Test for overall effect: Z = 4.18 (P < 0.0001)								
1.1.2 Number of neurorehabilitation principles < 8								
Ang 2014	7.2	2.3	8	4.9	4.1	7	1.7%	0.66 [-0.39, 1.72]
Askin 2018	2.25	6.3	18	0.5	7.25	20	3.3%	0.25 [-0.39, 0.89]
Cameirao 2011	84.6	18.4	8	66.9	22.9	8	1.8%	0.81 [-0.23, 1.84]
Housman 2009	3.3	2.4	14	2.2	2.6	14	2.7%	0.43 [-0.32, 1.18]
Kim 2018	10.5	8.58	11	12	11.11	8	2.1%	-0.15 [-1.06, 0.76]
Kottink 2014	1.5	2.3	8	2.3	2.8	10	2.1%	-0.29 [-1.23, 0.64]
Kwon 2012	2.61	3.36	13	5.47	7.7	13	2.6%	-0.47 [-1.25, 0.31]
Liao 2012	6.3	5.64	10	1.3	7.92	10	2.1%	0.70 [-0.21, 1.61]
Nijenhuis 2016	0.3	19.02	9	2	16.63	10	2.2%	-0.09 [-0.99, 0.81]
Prange 2015	7.9	8.3	33	10.2	9.6	33	4.2%	-0.25 [-0.74, 0.23]
Wolf 2015	9.3	25.76	47	9.6	24.98	45	4.7%	-0.01 [-0.42, 0.40]
Subtotal (95% CI)			**179**			**178**	**29.6%**	**0.05 [-0.17, 0.27]**
Heterogeneity: Tau² = 0.01; Chi² = 10.73, df = 10 (P = 0.38); I² = 7%								
Test for overall effect: Z = 0.47 (P = 0.64)								
Total (95% CI)			**692**			**687**	**100.0%**	**0.32 [0.16, 0.48]**
Heterogeneity: Tau² = 0.10; Chi² = 64.45, df = 34 (P = 0.001); I² = 47%								
Test for overall effect: Z = 3.87 (P = 0.0001)								
Test for subgroup differences: Chi² = 5.73, df = 1 (P = 0.02), I² = 82.6%								



Supplementary Figure 5. Sensitivity analysis: use of a different correlation coefficient value (0.9). Forest plot of UL motor function as measured by the FMA-UE: studies using a serious game fulfilling ≥ 8 neurorehabilitation principles versus studies using a serious game fulfilling < 8 neurorehabilitation principles.

	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
1.2.1 Number of neurorehabilitation principles > or = 8								
Aprile 2020	8.5	8.0668	91	8.57	8.0222	99	3.5%	-0.01 [-0.29, 0.28]
Choi 2016	19.08	9.71	12	9.67	10.26	12	2.6%	0.91 [0.06, 1.76]
Dehem 2019	19.5	13.68	15	10.8	14.4	17	2.9%	0.60 [-0.11, 1.31]
Duff 2012	1.48	3.2	11	6.83	3.55	10	2.4%	-1.52 [-2.52, -0.53]
Henrique 2019	14.69	0.67	16	9.07	1.34	15	1.6%	5.22 [3.66, 6.78]
Hung 2019	3.5	6.37	17	3.38	8.18	16	2.9%	0.02 [-0.67, 0.70]
Jang 2005	7	3.12	5	2.4	1.96	5	1.6%	1.59 [0.06, 3.13]
Kiper 2011	9.8	7.41	40	1.6	7.72	40	3.3%	1.07 [0.60, 1.54]
Kiper 2014	6.8	6.45	23	3.2	7.64	21	3.1%	0.50 [-0.10, 1.10]
Kiper 2018	9.72	7.74	68	3.14	7.76	68	3.4%	0.84 [0.49, 1.20]
Laffont 2019	24.1	14.8	25	17.8	14.6	26	3.1%	0.42 [-0.13, 0.98]
Lee 2016 (a)	7	7.78	13	-0.31	8.16	13	2.7%	0.89 [0.08, 1.70]
Lee 2018	8.2	4.78	15	2.33	3.6	15	2.7%	1.35 [0.55, 2.15]
Levin 2012	5	5.3	6	1	5.67	6	2.1%	0.67 [-0.51, 1.85]
Norouzi-Gheidari 2019	2.1	8.2	9	-0.2	5.37	9	2.5%	0.32 [-0.62, 1.25]
Ogun 2019	6.91	3.85	33	1.5	3.86	32	3.2%	1.39 [0.84, 1.93]
Oh 2019	1.9	3	17	2.1	2	14	2.9%	-0.07 [-0.78, 0.63]
Park 2019	1.9	2.8	12	2.1	2.7	13	2.7%	-0.07 [-0.86, 0.71]
Piron 2009	5.1	3.47	18	2.2	2.11	18	2.9%	0.99 [0.29, 1.68]
Piron 2010	7.3	4.93	27	2.6	4.34	20	3.0%	0.99 [0.37, 1.60]
Shin 2014	11.7	5.01	9	6.3	5.57	7	2.3%	0.97 [-0.09, 2.03]
Shin 2015	4.63	4.7	16	5.57	7.25	16	2.9%	-0.15 [-0.84, 0.54]
Shin 2016	4.9	1	24	1.4	0.8	22	2.4%	3.78 [2.79, 4.77]
Thielbar 2014	1.7	4.54	7	1.7	6.44	7	2.3%	0.00 [-1.05, 1.05]
Tomic 2017	18	9.4	13	7.5	5.5	13	2.6%	1.32 [0.46, 2.18]
Yin 2014	15.33	12.86	11	13.63	15.09	12	2.7%	0.12 [-0.70, 0.94]
Subtotal (95% CI)			**553**			**546**	**70.2%**	**0.76 [0.43, 1.10]**
Heterogeneity: Tau² = 0.57; Chi² = 150.70, df = 25 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 4.53 (P < 0.00001)								
1.2.2 Number of neurorehabilitation principles < 8								
Ang 2014	7.2	2.3	8	4.9	4.1	7	2.3%	0.66 [-0.39, 1.72]
Askin 2018	2.25	4.46	18	0.5	5.13	20	3.0%	0.36 [-0.29, 1.00]
Cameirao 2011	84.6	18.4	8	66.9	22.9	8	2.3%	0.81 [-0.23, 1.84]
Housman 2009	3.3	2.4	14	2.2	2.6	14	2.8%	0.43 [-0.32, 1.18]
Kim 2018	10.5	6.34	11	12	7.86	8	2.5%	-0.20 [-1.12, 0.71]
Kottink 2014	1.5	2.3	8	2.3	2.8	10	2.5%	-0.29 [-1.23, 0.64]
Kwon 2012	3.36	2.75	13	5.47	7.07	13	2.8%	-0.38 [-1.16, 0.40]
Liao 2012	6.3	3.99	10	1.3	5.75	10	2.5%	0.97 [0.03, 1.91]
Nijenhuis 2016	0.3	13.49	9	2	12.27	10	2.5%	-0.13 [-1.03, 0.78]
Prange 2015	7.9	8.3	33	10.2	9.6	33	3.3%	-0.25 [-0.74, 0.23]
Wolf 2015	9.3	19.34	47	9.6	18.86	45	3.4%	-0.02 [-0.42, 0.39]
Subtotal (95% CI)			**179**			**178**	**29.8%**	**0.09 [-0.15, 0.34]**
Heterogeneity: Tau² = 0.03; Chi² = 12.61, df = 10 (P = 0.25); I² = 21%								
Test for overall effect: Z = 0.74 (P = 0.46)								
Total (95% CI)			**732**			**724**	**100.0%**	**0.58 [0.32, 0.83]**
Heterogeneity: Tau² = 0.47; Chi² = 181.60, df = 36 (P < 0.00001); I² = 80%								
Test for overall effect: Z = 4.39 (P < 0.0001)								
Test for subgroup differences: Chi² = 10.15, df = 1 (P = 0.001), I² = 90.1%								

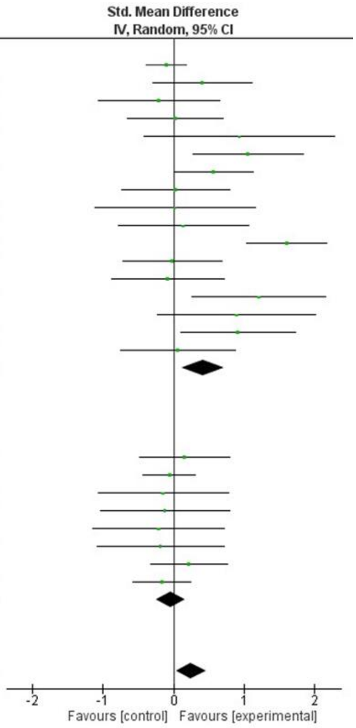


Effect of rehabilitation through serious games on UL activity

In total, rehabilitation using serious games led to significantly better improvements, of low effect size, in UL activity compared to conventional treatment (SMD = 0,25; 95% CI = 0,05 to 0,46; P = 0.02) (Figure 4). In a similar way to results regarding UL function, subgroup analysis showed significantly better improvements, of moderate effect size, only for interventions that fulfilled 8 or more neurorehabilitation principles (SMD = 0.42; 95% CI = 0,12 to 0,72; P = 0.006). Differences among subgroups were statistically significant (P = 0.01). Total results indicated moderate heterogeneity between studies (I^2 = 56 %). Additional subgroup analysis based on stroke stage did not reach statistical significance for neither subacute or chronic stage after stroke (Supplementary Figure 6).

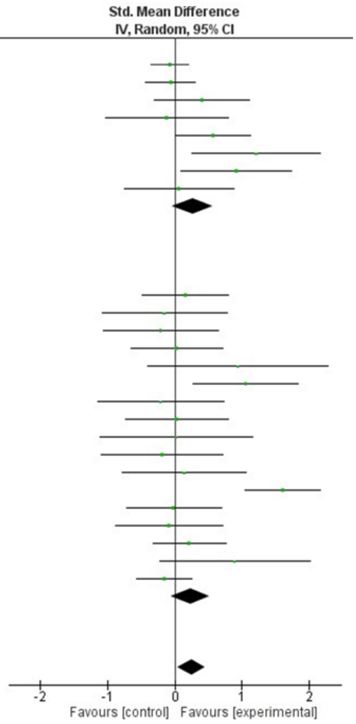
Figure 4. Forest plot of UL activity as measured by the ARAT, BBT, WMFT: studies using a serious game fulfilling ≥8 neurorehabilitation principles versus studies using a serious game fulfilling < 8 neurorehabilitation principles.

	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
2.1.1 Number of neurorehabilitation principles > or = 8								
Aprile 2020	6.04	8.547	91	6.7	4.84	99	7.1%	-0.10 [-0.38, 0.19]
Dehem 2019	6.5	9.14	15	3.1	7.26	17	4.2%	0.40 [-0.30, 1.11]
Duff 2012	0.47	0.36	11	0.54	0.28	10	3.4%	-0.21 [-1.07, 0.65]
Hung 2019	0.085	0.41	17	0.07	0.72	16	4.3%	0.03 [-0.66, 0.71]
Jang 2005	4	4.84	5	-1.6	5.91	5	1.8%	0.94 [-0.41, 2.28]
Jo 2012	8.5	7.7	15	2	3.29	14	3.8%	1.05 [0.27, 1.84]
Laffont 2019	15.7	16.3	25	7.4	12.2	26	5.1%	0.57 [0.01, 1.13]
Lee 2016 (a)	2.85	10.47	13	2.54	10.48	13	3.9%	0.03 [-0.74, 0.80]
Levin 2012	0.5	17.23	6	0.1	13.38	6	2.4%	0.02 [-1.11, 1.16]
Norouzi-Gheidari 2019	0.2	14.66	9	-1.6	9.18	9	3.1%	0.14 [-0.79, 1.07]
Ogun 2019	8.34	4.78	33	1.25	3.89	32	5.1%	1.60 [1.04, 2.17]
Oh 2019	3.4	4.9	17	3.5	7.2	14	4.2%	-0.02 [-0.72, 0.69]
Park 2019	4.3	5.9	12	4.8	5.9	12	3.7%	-0.08 [-0.88, 0.72]
Rogers 2019	17.3	8.6	10	8.4	5.3	11	3.0%	1.21 [0.26, 2.16]
Thielbar 2014	3.1	5.6	7	-3.5	8.01	7	2.4%	0.89 [-0.22, 2.01]
Tomic 2017	14.1	7.9	13	6.7	7.8	13	3.6%	0.91 [0.10, 1.73]
Yin 2014	18.34	19.99	11	17.02	21	12	3.6%	0.06 [-0.76, 0.88]
Subtotal (95% CI)			**310**			**316**	**64.8%**	**0.42 [0.12, 0.72]**
Heterogeneity: Tau² = 0.23; Chi² = 44.91, df = 16 (P = 0.0001); I² = 64%								
Test for overall effect: Z = 2.77 (P = 0.006)								
2.1.2 Number of neurorehabilitation principles < 8								
Askin 2018	1.75	13.3	18	0	7.81	20	4.6%	0.16 [-0.48, 0.80]
Brunner 2017	11.9	12.01	57	12.6	11.83	55	6.5%	-0.06 [-0.43, 0.31]
Crosbie 2012	1.5	4.93	9	2.9	11.73	9	3.1%	-0.15 [-1.07, 0.78]
Kim 2018	8.4	8.68	11	9.6	10.35	8	3.2%	-0.12 [-1.03, 0.79]
Kottink 2014	3.9	4.9	8	5	5.1	10	3.1%	-0.21 [-1.14, 0.72]
Nijenhuis 2016	-0.37	21.77	9	3.23	15.24	10	3.2%	-0.18 [-1.09, 0.72]
Schuster-Amft 2018	24.37	15.2	22	20.17	21.5	32	5.2%	0.22 [-0.33, 0.76]
Wolf 2015	5.1	22.85	47	8.8	23.19	45	6.2%	-0.16 [-0.57, 0.25]
Subtotal (95% CI)			**181**			**189**	**35.2%**	**-0.04 [-0.25, 0.16]**
Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 7 (P = 0.97); I² = 0%								
Test for overall effect: Z = 0.42 (P = 0.68)								
Total (95% CI)			**491**			**505**	**100.0%**	**0.25 [0.05, 0.46]**
Heterogeneity: Tau² = 0.14; Chi² = 54.04, df = 24 (P = 0.0004); I² = 56%								
Test for overall effect: Z = 2.39 (P = 0.02)								
Test for subgroup differences: Chi² = 6.35, df = 1 (P = 0.01), I² = 84.2%								



Supplementary Figure 6. Forest plot of UL activity as measured by the ARAT, BBT, WMFT: studies in the subacute phase after stroke versus studies in the chronic phase after stroke.

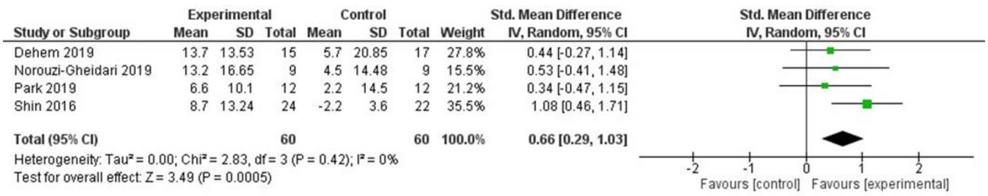
	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
2.3.1 Subacute								
Aprile 2020	6.04	8.547	91	6.7	9.3258	99	7.1%	-0.07 [-0.36, 0.21]
Brunner 2017	11.9	12.01	57	12.6	11.83	55	6.5%	-0.06 [-0.43, 0.31]
Dehem 2019	6.5	9.14	15	3.1	7.26	17	4.2%	0.40 [-0.30, 1.11]
Kim 2018	8.4	8.68	11	9.6	10.35	8	3.2%	-0.12 [-1.03, 0.79]
Laffont 2019	15.7	16.3	25	7.4	12.2	26	5.1%	0.57 [0.01, 1.13]
Rogers 2019	17.3	8.6	10	8.4	5.3	11	3.0%	1.21 [0.26, 2.16]
Tomic 2017	14.1	7.9	13	6.7	7.8	13	3.6%	0.91 [0.10, 1.73]
Yin 2014	18.34	19.99	11	17.02	21	12	3.6%	0.06 [-0.76, 0.88]
Subtotal (95% CI)			**233**			**241**	**36.4%**	**0.27 [-0.04, 0.57]**
Heterogeneity: Tau² = 0.09; Chi² = 14.76, df = 7 (P = 0.04); I² = 53%								
Test for overall effect: Z = 1.73 (P = 0.08)								
2.3.2 Chronic								
Askin 2018	1.75	13.3	18	0	7.81	20	4.6%	0.16 [-0.48, 0.80]
Crosbie 2012	1.5	4.93	9	2.9	11.73	9	3.1%	-0.15 [-1.07, 0.78]
Duff 2012	0.47	0.36	11	0.54	0.28	10	3.4%	-0.21 [-1.07, 0.65]
Hung 2019	0.085	0.41	17	0.07	0.72	16	4.3%	0.03 [-0.66, 0.71]
Jang 2005	4	4.84	5	-1.6	5.91	5	1.8%	0.94 [-0.41, 2.28]
Jo 2012	8.5	7.7	15	2	3.29	14	3.8%	1.05 [0.27, 1.84]
Kottink 2014	3.9	4.9	8	5	5.1	10	3.1%	-0.21 [-1.14, 0.72]
Lee 2016 (a)	2.85	10.47	13	2.54	10.48	13	3.9%	0.03 [-0.74, 0.80]
Levin 2012	0.5	17.23	6	0.1	13.38	6	2.4%	0.02 [-1.11, 1.16]
Nijenhuis 2016	-0.37	21.77	9	3.23	15.24	10	3.2%	-0.18 [-1.09, 0.72]
Norouzi-Gheidari 2019	0.2	14.66	9	-1.6	9.18	9	3.1%	0.14 [-0.79, 1.07]
Ogun 2019	8.34	4.78	33	1.25	3.89	32	5.1%	1.60 [1.04, 2.17]
Oh 2019	3.4	4.9	17	3.5	7.2	14	4.2%	-0.02 [-0.72, 0.69]
Park 2019	4.3	5.9	12	4.8	5.9	12	3.7%	-0.08 [-0.88, 0.72]
Schuster-Amft 2018	24.37	15.2	22	20.17	21.5	32	5.2%	0.22 [-0.33, 0.76]
Thielbar 2014	3.1	5.6	7	-3.5	8.01	7	2.4%	0.89 [-0.22, 2.01]
Wolf 2015	5.1	22.85	47	8.8	23.19	45	6.2%	-0.16 [-0.57, 0.25]
Subtotal (95% CI)			**258**			**264**	**63.6%**	**0.23 [-0.05, 0.52]**
Heterogeneity: Tau² = 0.20; Chi² = 38.16, df = 16 (P = 0.001); I² = 58%								
Test for overall effect: Z = 1.59 (P = 0.11)								
Total (95% CI)			**491**			**505**	**100.0%**	**0.25 [0.05, 0.46]**
Heterogeneity: Tau² = 0.13; Chi² = 53.48, df = 24 (P = 0.0005); I² = 55%								
Test for overall effect: Z = 2.41 (P = 0.02)								
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%								



Effect of rehabilitation through serious games on participation

In total, rehabilitation using serious games led to significantly better improvements, of large effect size, in participation compared to conventional treatment (SMD = 0,66; 95% CI = 0,29 to 1,03; P = 0.0005) (Figure 5). No significant heterogeneity was present (I^2 = 0 %). All trials included in this analysis used a serious game that complied with 8 or more neurorehabilitation principles.

Figure 5. Forest plot of participation as measured by the social participation subscale of the SIS.

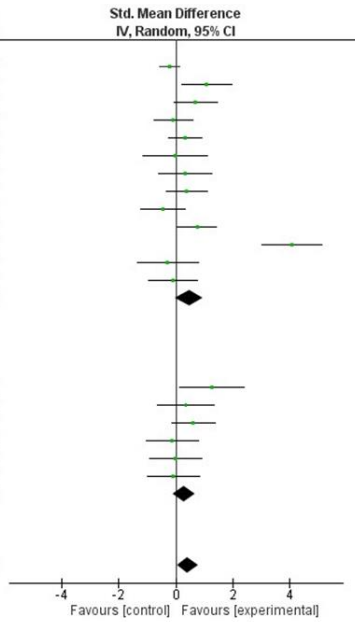


Analysis of Follow-up Data

Separate analyses were conducted regarding follow-up data for each ICF-WHO component. Only half of the studies included in the quantitative synthesis (50%) performed follow-up evaluations. Among them, length of follow-up period ranged from 1 month to 6 months with a mean (SD) of 2.3 months (1.86). An overall tendency towards improvement for interventions using serious games regarding all ICF-WHO components was observed (Supplementary Figures 7, 8 and 9). Total estimates concerning UL function indicate effect retention to follow-up in favour of the experimental group of moderate effect size (SMD = 0,42; 95% CI = 0,05 to 0,79; P = 0.03). Results didn't reach statistical significance regarding UL activity and participation.

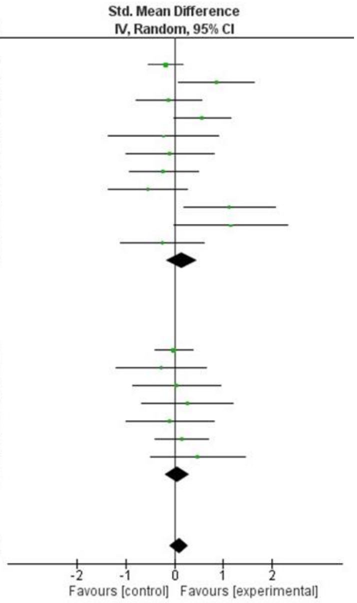
Supplementary Figure 7. Follow-up evaluation. Forest plot of UL motor function as measured by the FMA-UE: studies using a serious game fulfilling ≥ 8 neurorehabilitation principles versus studies using a serious game fulfilling < 8 neurorehabilitation principles.

	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
1.5.1 Number of neurorehabilitation principles > or = 8								
Aprile 2020	13.9	13.31	58	16.6	12.88	64	6.8%	-0.21 [-0.56, 0.15]
Choi 2016	29.25	13.91	12	13.17	14.88	12	5.2%	1.08 [0.21, 1.94]
Dehem 2019	24.7	20.35	15	10	20.71	13	5.5%	0.70 [-0.07, 1.46]
Hung 2019	3.5	9.58	17	4.48	11.98	16	5.8%	-0.09 [-0.77, 0.59]
Laffont 2019	31.2	15.8	23	25.6	16.3	23	6.2%	0.34 [-0.24, 0.93]
Levin 2012	4	7.1	6	4.1	7.89	6	4.3%	-0.01 [-1.14, 1.12]
Norouzi-Gheidari 2019	3	11.29	9	-0.4	8.02	9	5.0%	0.33 [-0.60, 1.26]
Oh 2019	3.9	4.9	17	2.3	2.3	14	5.7%	0.39 [-0.32, 1.11]
Park 2019	2.5	3.7	12	5.6	8.6	13	5.4%	-0.45 [-1.24, 0.35]
Piron 2009	4.6	4.8	18	1.5	3.1	18	5.8%	0.75 [0.07, 1.43]
Shin 2016	5.3	1.1	24	1.3	0.8	22	4.6%	4.06 [3.02, 5.10]
Thielbar 2014	1.3	5.85	7	3	5.79	7	4.6%	-0.27 [-1.33, 0.78]
Yin 2014	22.63	21.7	11	25.08	26.64	10	5.2%	-0.10 [-0.95, 0.76]
Subtotal (95% CI)			**229**			**227**	**70.3%**	**0.47 [-0.02, 0.96]**
Heterogeneity: Tau² = 0.65; Chi² = 70.33, df = 12 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 1.86 (P = 0.06)								
1.5.2 Number of neurorehabilitation principles < 8								
Ang 2014	9.7	2.9	8	3.6	5.9	7	4.3%	1.27 [0.12, 2.41]
Cameirao 2011	79.1	19	8	72	18.8	8	4.8%	0.36 [-0.64, 1.35]
Housman 2009	3.6	3.9	14	1.5	2.7	14	5.6%	0.61 [-0.15, 1.37]
Kim 2018	17	7.08	11	18.1	10.9	8	5.0%	-0.12 [-1.03, 0.79]
Kottink 2014	4	5	8	4	3.2	10	5.0%	0.00 [-0.93, 0.93]
Nijenhuis 2016	0.17	18.89	9	1.57	16.63	10	5.1%	-0.08 [-0.98, 0.83]
Subtotal (95% CI)			**58**			**57**	**29.7%**	**0.30 [-0.08, 0.69]**
Heterogeneity: Tau² = 0.01; Chi² = 5.26, df = 5 (P = 0.39); I² = 5%								
Test for overall effect: Z = 1.54 (P = 0.12)								
Total (95% CI)			**287**			**284**	**100.0%**	**0.42 [0.05, 0.79]**
Heterogeneity: Tau² = 0.49; Chi² = 75.61, df = 18 (P < 0.00001); I² = 76%								
Test for overall effect: Z = 2.23 (P = 0.03)								
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%								



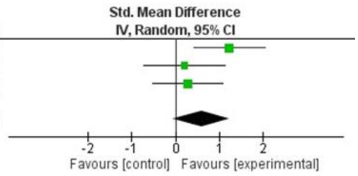
Supplementary Figure 8. Follow-up evaluation. Forest plot of UL activity as measured by the ARAT, BBT, WMFT: studies using a serious game fulfilling ≥ 8 neurorehabilitation principles versus studies using a serious game fulfilling < 8 neurorehabilitation principles.

	Experimental			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
2.2.1 Number of neurorehabilitation principles > or = 8								
Aprile 2020	11.6	12.37	58	13.8	11.96	64	13.5%	-0.18 [-0.54, 0.18]
Dehem 2019	9.7	11.77	15	1.3	5.89	13	5.0%	0.86 [0.08, 1.64]
Hung 2019	0.015	0.37	17	0.08	0.72	16	6.2%	-0.11 [-0.80, 0.57]
Laffont 2019	23.8	16.7	23	14.4	15.5	23	7.6%	0.57 [-0.02, 1.16]
Levin 2012	2.4	17.34	6	6.3	14.43	6	2.7%	-0.23 [-1.36, 0.91]
Norouzi-Gheidari 2019	1.5	13.23	9	2.7	10.45	10	4.0%	-0.10 [-1.00, 0.80]
Oh 2019	4.3	8.3	17	6.3	9.1	14	5.8%	-0.22 [-0.93, 0.49]
Park 2019	5.3	6.6	12	10.1	10.1	12	4.7%	-0.54 [-1.36, 0.27]
Rogers 2019	19	9.31	10	9.4	6.99	11	3.7%	1.13 [0.19, 2.06]
Thielbar 2014	4.8	5.34	7	-2.8	6.84	7	2.6%	1.16 [-0.00, 2.32]
Yin 2014	28.97	23.62	11	34.17	16.17	10	4.3%	-0.24 [-1.10, 0.62]
Subtotal (95% CI)			**185**			**186**	**60.1%**	**0.14 [-0.18, 0.47]**
Heterogeneity: Tau² = 0.15; Chi² = 20.85, df = 10 (P = 0.02); I² = 52%								
Test for overall effect: Z = 0.86 (P = 0.39)								
2.2.2 Number of neurorehabilitation principles < 8								
Brunner 2017	17.2	11.4	50	17.3	11.59	52	12.5%	-0.01 [-0.40, 0.38]
Crosbie 2012	0.8	5.1	9	3.4	11.76	9	3.8%	-0.27 [-1.20, 0.66]
Kim 2018	17.3	11.76	11	16.7	13.48	8	3.9%	0.05 [-0.87, 0.96]
Kottink 2014	5.6	8.9	8	3.7	4.8	10	3.7%	0.26 [-0.67, 1.20]
Nijenhuis 2016	0.33	21.77	9	2.03	13.45	10	4.0%	-0.09 [-0.99, 0.81]
Schuster-Amft 2018	24.77	17.63	22	21.7	21.5	32	8.5%	0.15 [-0.39, 0.69]
Zondervan 2016	0.7	2.3	9	-0.6	2.9	8	3.5%	0.48 [-0.49, 1.44]
Subtotal (95% CI)			**118**			**129**	**39.9%**	**0.06 [-0.20, 0.31]**
Heterogeneity: Tau² = 0.00; Chi² = 1.71, df = 6 (P = 0.94); I² = 0%								
Test for overall effect: Z = 0.44 (P = 0.66)								
Total (95% CI)			**303**			**315**	**100.0%**	**0.09 [-0.10, 0.29]**
Heterogeneity: Tau² = 0.04; Chi² = 22.57, df = 17 (P = 0.16); I² = 25%								
Test for overall effect: Z = 0.94 (P = 0.35)								
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%								



Supplementary Figure 9. Follow-up evaluation. Forest plot of participation as measured by the social participation subscale of the SIS.

	Experimental			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Dehem 2019	23.6	14.61	15	2.3	18.95	13	34.6%	1.23 [0.41, 2.05]
Norouzi-Gheidari 2019	6.9	16.45	9	3.8	11.09	9	30.1%	0.21 [-0.72, 1.14]
Park 2019	5.2	9.9	12	2.3	9.5	12	35.3%	0.29 [-0.52, 1.09]
Total (95% CI)			**36**			**34**	**100.0%**	**0.59 [-0.06, 1.25]**
Heterogeneity: Tau² = 0.15; Chi² = 3.55, df = 2 (P = 0.17); I² = 44%								
Test for overall effect: Z = 1.78 (P = 0.08)								



3.5 Discussion

Main results

This systematic review and meta-analysis showed results in favour of rehabilitation using, purpose-built, serious games on UL motor function, UL activity and participation after stroke compared to conventional treatment. Moreover, long term effect retention was significantly maintained regarding UL function. Irrespective of the technological device used, serious games that complied with more than 8 out of 11 neurorehabilitation principles showed better overall effects.

Previous studies on effectiveness of VRS/ commercial video-games for UL rehabilitation after stroke

Previous work on the use of VRS and commercial video-games for UL rehabilitation after stroke demonstrated similar results [61, 113]. Yet, to date, usage and efficacy of game-based interventions for UL rehabilitation after stroke remain controversial [131, 132]. Initially, a meta-analysis by Saposnik et al., combining observational studies and RCT, suggested improvements in UL strength and motor function after stroke [133]. However, this review focused on various VRS, including commercial video-games designed by the entertainment industry, not specifically developed for rehabilitation. In addition, no statistically significant differences were observed concerning UL activity outcomes and no analysis was conducted regarding ICF-WHO participation component due to limited available data.

Two other groups conducted systematic reviews on a similar topic [134, 135]. However, both reviews included studies concerning not only UL rehabilitation but also gait and balance, making it difficult to draw conclusions regarding the UL. Palma et al., solely relying on qualitative synthesis, supported positive findings on function [134]. Results were inconclusive regarding activity and participation components and further interpretation was limited due to lack of quantitative synthesis. Then, a meta-analysis by Lohse et al. showed positive effects in favour of VR-based interventions regarding three ICF-WHO components [135]. However, analysis was restricted to therapies that did not include robotic assistance. Furthermore, analyses through meta-regressions did not point out significant differences in outcomes between commercially available and custom-built systems. Two updated Cochrane reviews covered broader aspects of VR and robotics in UL rehabilitation after stroke [36, 111]. In the review by Mehrholz et al., high quality evidence supports better improvements in ADL, arm function and arm strength in favour of RAT [36]. Nonetheless, effects of robotic training performed in form of a serious game were not studied. Then, a review by Laver et al. on VR-based interventions, demonstrated equivalent improvements in UL function and activity when comparing time-matched interventions [111]. Notably, UL function and activity outcomes were pooled in one common analysis instead of distinguishing effects in terms of the two ICF-WHO components. Further analyses in subgroups suggested better results when specific systems designed for rehabilitation were employed compared to off-the-shelf commercial video-games, although differences did not reach statistical significance. Finally, two recent reviews showed improvements on both UL function and activity in groups receiving VR/gaming-based training after stroke [59, 61]. However, both reviews studied broader aspects of VR-based interventions and their scope was not delimited to specific use of serious games. Karamians et al. suggested that interventions with gaming components further promote recovery compared to those providing visual feedback only [59]. Then, Maier et al. distinguished VRS specifically built for rehabilitation purposes from others destined to generic use [61]. Results illustrated that, when compared to conventional therapy, interventions specifically designed based on elements enhancing neural plasticity led to significantly better results [61]. Additionally, it was suggested that custom-made interventions, in comparison to non-specific interventions, comply better with a series of neurorehabilitation principles.

Adherence to neurorehabilitation principles of interventions using serious games for UL rehabilitation after stroke

To this date, UL stroke recovery through games developed specifically for rehabilitation and implemented on diverse systems, has not been explicitly reviewed. In addition, most recent reviews delimit their scope in technological terms by considering interventions based on the devices being used [42, 59, 61]. Some authors characterise comparison between studies using different devices as difficult [136]. However, a holistic overview of serious games, regardless of the technology used, is important in order to better understand their added value in UL rehabilitation after stroke. Comparison between studies using systems with different technical specificities, mainly in hardware, is challenging. Nonetheless, interventions through serious games implemented on different devices may share similarities. Indeed, all studies included in our review perform non-invasive treatments. Then, gamification and adaptability of interventions, to the patients' impairments and performance, aim to maintain motivation throughout therapy sessions [137]. Additionally, all these systems have the potential to give access to kinematic data allowing objective assessment, evaluating real-time performance and tracking UL recovery [138-140]. Finally, all interventions stimulate recovery through adherence to common neurorehabilitation principles. In fact, comparison across different types of technologies and treatment modalities leads to identification of common 'active ingredients' in terms of effective rehabilitation [61].

In accordance with recent literature, this review contributes to identifying a rationale regarding efficacy of interventions in UL rehabilitation after stroke. Our results point out that even in a group of interventions specifically developed for rehabilitation purposes, differences in outcomes may be explained depending on higher adherence to neurorehabilitation principles. Furthermore, even though most interventions seem to fulfil certain principles (task-specific practice, variable practice, massed practice), it seems that clusters of principles met among serious games may lead to differences in efficacy. For instance, our findings suggest that providing feedback during therapy appears to be an important characteristic that interventions using serious games should satisfy. Further, to what degree each individual principle contributes in efficacy is difficult to study. However, it appears that the more an intervention adheres to principles, the better the expected outcomes can be regarding motor recovery.

To the best of our knowledge, this systematic review is the first to address, in a non-fragmented way, efficacy of specifically designed gaming interventions in UL rehabilitation after stroke. Our results confirm current trends favouring custom-made rehabilitation systems and gamification of interventions. Positive findings concerning function and activity have already been reported in previous reviews [59, 61]. It is worth noting that this review shows encouraging results in participation outcomes indicating, therefore, improvements in three ICF-WHO components.

Strengths and limitations

In a rapidly emerging field, 40% of studies included in our review were published within the last 3 years. Quantitative synthesis was performed by only using RCT of moderate to high methodological quality. However, this was not feasible for two studies due to unavailable data. Additionally, even though our work was conducted according to PRISMA guidelines for systematic reviews, no methods were used to detect unpublished trials. Also, publication bias was only assessed through funnel plot graphic representation which nonetheless did not indicate asymmetry. Heterogeneity across studies was moderate to high regarding UL function and activity outcomes. Tis may be partially due to variation of elements such as patient characteristics, duration of interventions and evaluation timepoints. Heterogeneity was addressed by using a random effects model for meta-analyses and by conducting additional analyses. Even though heterogeneity levels remained moderate, our results were little affected by changes in methods or outliers, indicating robustness.

Perspectives

Our work offers some suggestions regarding clinical practice and future research. Interventions using serious games may be encouraged and integrated in UL rehabilitation programs during subacute and chronic stage after stroke. Specifications regarding dosage, duration and selection of patients that could benefit most from these treatments need further investigation. In addition, serious games should be explored in terms of ways to provide self- or tele-rehabilitation.

From a research point of view, new developments in gaming interventions can take into consideration adherence to neurorehabilitation principles. In accordance with our findings, future developments of interventions in UL stroke rehabilitation ought to comply with as many neurorehabilitation principles as possible. Future work should study how variations in clusters of these principles may influence differently specific aspects of motor or cognitive rehabilitation. Also, richness of kinematic data, accessible through technological devices on which games are implemented, open new perspectives in assessment and follow-up of stroke patients. In our review, only 11% of studies used kinematic data, complementary to clinical rating scales, for UL function evaluation. Finally, few studies (11%) included in our review reported cognitive outcomes. Since motor performance and functional recovery can be influenced by cognitive determinants [17, 141], combined assessment of all these aspects should be further considered in future work.

3.6 Conclusion

In conclusion, this systematic review and meta-analysis showed that post-stroke UL rehabilitation through serious games, implemented on various types of technological devices, showed better improvements, compared to conventional treatment, on three ICF-WHO components. Long term effect retention was maintained for UL function. Irrespective of the technological system used, serious games that complied with more than 8 out of 11 neurorehabilitation principles led to better overall effects. Our findings emphasize the importance of adherence to neurorehabilitation principles in order to improve efficacy of interventions in UL rehabilitation after stroke.

CHAPTER IV – Self-Rehabilitation for Post-Stroke Motor Function and Activity: A Systematic Review and Meta-Analysis

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Published in Neurorehabilitation Neural Repair 2021;35(12):1043-1058.

doi:10.1177/15459683211048773

4.1 Abstract

Background: Due to an increasing stroke incidence, a lack of resources to implement effective rehabilitation and a significant proportion of patients with remaining impairments after treatment, there is a rise in demand for effective and prolonged rehabilitation. Development of self-rehabilitation programs provides an opportunity to meet these increasing demands.

Objective: The primary aim of this meta-analysis was to determine the effect of self-rehabilitation on motor outcomes, in comparison to conventional rehabilitation, among patients with stroke. The secondary aim was to assess the influence of trial location (continent), technology, time since stroke (acute/subacute vs chronic), dose (total training duration > vs ≤ 15 hours), and intervention design (self-rehabilitation in addition/substitution to conventional therapy) on effect of self-rehabilitation.

Methods: Studies were selected if participants were adults with stroke; the intervention consisted of a self-rehabilitation program defined as a tailored program where for most of the time, the patient performed rehabilitation exercises independently; the control group received conventional therapy; outcomes included motor function and activity; and the study was a randomized controlled trial with a PEDro score ≥5.

Results: Thirty-five trials were selected (2225 participants) and included in quantitative synthesis regarding motor outcomes. Trials had a median PEDro Score of 7 [6–8]. Self-rehabilitation programs were shown to be as effective as conventional therapy. Trial location, use of technology, stroke stage, and intervention design did not appear to have a significant influence on outcomes.

Conclusion: This meta-analysis showed low to moderate evidence that self-rehabilitation and conventional therapy efficacy was equally valuable for post-stroke motor function and activity.

Keywords: stroke, self-rehabilitation, new technologies, intervention design, trials location, review

4.2 Introduction

Each year, approximately 1.1 million Europeans suffer a stroke and in 2020, there was an estimated 9.5 million stroke survivors in Europe [181, 182]. By 2030, stroke prevalence is expected to rise by 35% [183]. Almost 80% of these patients present motor impairments and for half, these impairments will remain permanently [184, 185]. This leads to activity limitation, social participation restriction, and affects quality of life. Therefore, there is an urgent need to improve stroke outcome by providing new additional and prolonged neurological rehabilitation methods. Currently, a large proportion of patients does not achieve the recommended amount of physical activity (30 min per day) and do not spend sufficient time on rehabilitation [186, 187]. Hospital resources and healthcare systems are often limited [188]. This has led to the development of new cost-effective rehabilitation methods such as self-rehabilitation [189-191].

In this review, we define self-rehabilitation as a tailored therapy program where for most of the time, the patient performs rehabilitation exercises independently to the presence of a clinician [192]. This definition of rehabilitation also includes clinical remote support that can be provided with technology and communication methods through video or written instructions. Self-rehabilitation programs can be delivered at hospital, in rehabilitation centers, in physical therapy firms, and at home. Examples of self-rehabilitation include home-based self-guided therapies, unsupervised technologically assisted rehabilitation, and some telerehabilitation programs where patients perform exercises independently to the presence of a clinician. To date, only one published systematic review has assessed the effects of self-rehabilitation on stroke [193]. Results showed that self-rehabilitation, which did not involve technology, appeared to be more effective than conventional therapy for arm function. However, this article assessed trials whose interventions were exclusively meant to rehabilitate UL motor function, rather than using the World Health Organization's

International Classification of Function, Disability, and Health (ICF-WHO) model to classify self-rehabilitation outcomes [89, 194, 195]. Furthermore, few of the studies included in the review compared self-rehabilitation to conventional therapy. Since the publication of this review, several new randomized controlled trials (RCT) have emerged. Another alternative cost-effective rehabilitation method that overlaps with self-rehabilitation is called telerehabilitation. Telerehabilitation can be defined as “the delivery of rehabilitation services via information and communication technologies” [196]. These programs of rehabilitation are often supervised by a therapist and conducted in the patient’s home through telecommunication devices (mobile phones, motion-capture systems, computers-based communication, etc) [197]. Telerehabilitation effects on post-stroke motor impairments remain promising, with several meta-analyses of RCTs showing similar results for telerehabilitation and conventional therapy for motor outcomes [198-201]. There are several unknown factors that may influence the efficacy of self-rehabilitation on adults with stroke. First, outcomes may change depending on the location of the trial. There is evidence that race and ethnicity influence stroke incidence and recovery [202] and access to clinics can influence the intensity of rehabilitation [203]. Second, the implementation of new technologies for post-stroke self-rehabilitation may influence outcomes. Several meta-analyses have highlighted a superiority of virtual reality and robot-assisted therapy compared to conventional therapy when provided under clinical supervision [24, 61]. Third, the influence of delay since stroke, dose and design of intervention (in addition or in substitution to conventional therapy) on self-rehabilitation remains unknown. Lastly, the implementation of strategies to improve adherence to treatment may also influence self-rehabilitation outcomes [204]. The primary aim of this meta-analysis was to compare the effect of self-rehabilitation with conventional therapy on motor outcome and activity among patients with stroke. We included both upper and lower limb motor function and activity according to the ICF-WHO model [194]. The secondary aim was to determine the influence of trial location (continent), use of technology, stroke stage (acute/subacute vs chronic), and dose or design of the intervention (self-rehabilitation in addition or in substitution to conventional therapy) on motor function and activity.

4.3 Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (Supplementary Materials 1) [205]. The protocol was registered with Prospero reference CRD42020188857.

Literature Search

Search strategies were made according to the PICO format for the databases Pubmed, Embase, Cochrane Library, and Scopus (Supplementary Material 2). In addition, author handsearching was made by examination of the grey literature (Google Scholar and PEDro) and by checking the literature citations of relevant systematic reviews.

Eligibility Criteria

Trials were included if all the following PICOs criteria were fulfilled: (P) participants were post-stroke adults (aged > 18 years; ischemic or haemorrhagic stroke; no underlying neurological disease, no restriction for stroke stage); (I) the intervention consisted of a motor self-rehabilitation program (tailored therapy program where for most of the time, the patient performs rehabilitation exercises independently to the presence of a clinician) designed for upper and/or lower limb recovery and was conducted in addition to or in substitution of conventional therapy (the treatment could be provided in the home or at the hospital, in partial or complete autonomy); (C) the control group received post-stroke conventional therapy; (O) relevant outcomes were measured to assess the ICF-WHO motor function or activity components and; (S) the study followed a RCT design, was written in English, French, or Spanish, was published before December 19th, 2020, and had a PEDro score superior or equal to 5.

Selection Process

All references issued from databases were exported into a reference management software (EndNote X9). After disposal of duplicates, a first selection based on titles and abstracts was conducted. Trials were retrieved and sorted by two independent investigators (authors G.E. and A.L.) according to the eligibility criteria. At the same time, hand-searching results were stored in a spreadsheet software. All full-text articles were then screened and selected following the same procedure. Lastly, a meeting was organized between the two reviewers to compare selection. For articles not selected by both investigators, a consensus was found through discussion.

Design Considerations to Improve Adherence to Self-Rehabilitation

Studies were assessed to determine whether their treatment intervention fulfilled considerations that improved adherence to self-rehabilitation. Based on the research reported by Argent et al., 2018 [204], five main considerations were extracted: the provisioning of real time sessions (face-to-face sessions or videoconferences), the use of sensing platforms, the provision of visual feedback performance, the definition of quantifiable objectives and the availability of written, or video-recorded instructions. A consideration was defined to be fulfilled only when the study explicitly mentioned it.

Data Extraction

Prior to data extraction, the methodological quality of each study was evaluated using the Cochrane Collaboration's Risk of Bias and the PEDro checklist [206]. The following characteristics were then collected: country in which the trial was conducted, number of participants, patient's mean age and stroke stage (acute: 6 months after stroke) [87], type and duration of the therapy for both intervention and control groups, adherence to self-rehabilitation (measured by the time spent performing exercises or the amount of patients that reached the number of recommended sessions), type of outcome measures according to the ICF-WHO framework and mean improvements (with standard deviations). For body function: the Fugl–Meyer, modified Ashworth Scale, Chedocke Arm and Hand Inventory, grip strength, Hand Function sub-score of the Stroke Impact Scale and kinematic data such as stability indicators were considered. For activity limitation: the Action Research Arm Test, Box and Block Test, Wolf Motor Function Test, Barthel Index, Functional Independence Measure, Nine Hole Peg Test, EQ-5D, 10 Meter Walking Test, 6 Minutes Walking Test, 2 Minutes Walking Test, Berg Balance Scale, and Timed Up and Go were considered. For participation, no information was extracted since too few studies measured it [89, 117]. When the information was not found in the full-text, authors were contacted.

Statistical Analysis

All studies whose motor outcomes were available and measured according to the ICF-WHO framework were considered for quantitative synthesis. Mean improvements were calculated from the pre-post intervention score differences. When several time-points were mentioned, the latest one was retained for the analysis. Related standard deviations were then estimated according to the Cochrane Handbook. If a study reported standard error values, standard deviations values were computed by multiplying the standard error values by the square root of the sample size within a group.

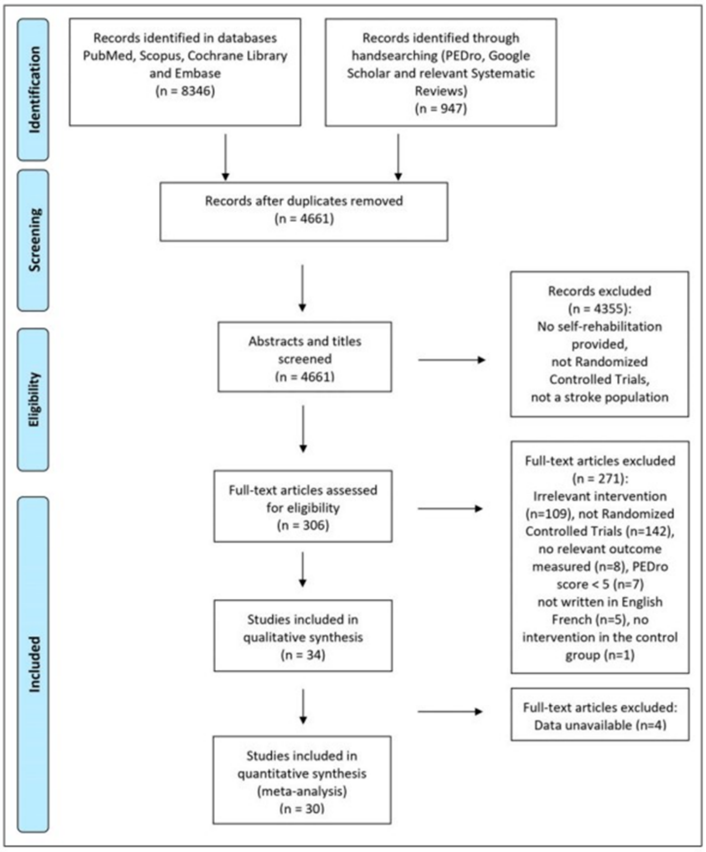
The RevMan 5.3 software was used to generate forest plots from trials included in the meta-analysis. Given that the scales used to assess outcomes were very heterogeneous, a standardized mean difference (SMD), and 95% confidence interval was calculated for each study. The SMD represents the ratio between the difference of mean effect between groups and the pooled standard deviation of the effect among participants.

Heterogeneity between the different trials was estimated using the I^2 test. As suggested by the Cochrane Handbook, heterogeneity was rated as non-significant for $I^2 < 30\%$, moderate for a I^2 between 30% and 50%, substantial for a I^2 between 50% and 75% and considerable for $I^2 > 75\%$. In case of heterogeneity, a further analysis was done using a random effect model. Publication bias was evaluated visually with funnel plot graphic representation. In case of funnel plot asymmetry or presence of outliers, a sensitivity analysis was conducted. The GRADEpro approach was used to assess the strength of the body evidence. This method enables a level of certainty regarding the overall results by taking into consideration the number of studies included in the analysis, the global study design, the risk of bias assessment, and the heterogeneity, directness, precision, and standard mean difference of the results. Subgroup analyses were conducted to see whether the location of the trial, the use of technology, the stroke stage (acute/subacute vs chronic), the total training duration (superior vs inferior or equal to 15 hours), and the design of the intervention (self-rehabilitation in addition or in substitution to conventional therapy) had an influence on outcome regarding the activity component of ICF-WHO framework. Additional subgroup analyses were performed to test difference between upper and lower limb self-rehabilitation effects on motor function and activity. Programs were not considered to be technologically assisted when the technology was only used to encode data, play video instructions or contact the therapist.

4.4 Results

The search identified a total of 9293 records. After removing duplicates, 4661 articles were screened based on their titles and abstracts. This resulted in the inclusion of 306 studies for full-text screening. Among these, 34 trials [189-190, 207-237] were retained for the qualitative synthesis and 30 were selected for the meta-analysis. A flow chart diagram illustrating the selection process is presented in Figure 1.

Figure 1. Selection process represented through a flow chart diagram.



Methodological Quality of the Included Studies

All randomized controlled trials (RCTs) were assessed with the PEDro checklist and Cochrane Collaboration Risk of Bias (Supplementary Materials 3 and 4). Trials had a median PEDro Score of 6.5 (6–8) and 85% of these were superior or equal to 6. The Cochrane Collaboration Risk of Bias assessment revealed that twenty-three RCTs (67%) reported the blinding of assessors, one RCT (3%) the blinding of participants and no RCTs the blinding of therapists. Among trials included in qualitative analysis, half declared using concealed allocation during the randomization process.

Study Characteristics

Extracted data of the included studies are presented in Table 1. The number of participants ranged from 10 to 306 with a mean age of 65.6 ± 5.8 years. Nineteen RCTs (56%) assessed patients with stroke in the chronic phase, fourteen (41%) in the subacute phase, and one (3%) did not provide enough information to classify the participants' stroke stage. Studies were conducted in four different continents (13 in Europe, 8 in Asia, 8 in America, and 5 in Oceania). Technologically assisted self-rehabilitation was provided in 23 RCTs (63%). Among these, fourteen (60%) focused on UL recovery, six (27%) on lower limb recovery, and three (13%) on full body recovery. Devices were tablets, computers, robots, non-immersive virtual reality systems, and functional electrical stimulation machines. In 20 RCTs, participants were instructed to practice their exercise at home according to therapist instructions. Non-technologically assisted self-rehabilitation was prescribed in twelve RCTs (35%). Among these, six (50%) focused on UL recovery, two (17%) on lower limb recovery, and four (33%) on full body recovery. Different types of therapy were provided: balance and walking programs, bimanual exercises, functional reaching tasks, functional grasping tasks, and unsupervised constraint-induced movement therapy. In twelve RCTs, participants were instructed to practice their exercise at home according to written or video guidance. Among the trials, 7 (58%) supplemented their intervention with conventional therapy. The total intervention dose ranged from 9 to 156 h with a mean duration of 40.5 ± 38.2 h and a total intervention duration from 2 weeks to 1 year. Twenty-nine trials (83%) provided interventions with a total duration superior or equal to 15 h, five (14%) provided less than 15 h of intervention, and one (3%) study was not precise enough to determine the total hours of intervention.

Table 1. Characteristics of Included Trials.

Authors	Participants	Age (mean)	Stroke onset (mean)	Country	Intervention	Intervention duration (mean)	Body function	Activity	Adherence	PEDro
Adie 2016	240	64.7 years	.9 month	UK	TSR: Unsupervised Wii training + CT	17 h	/	ARAT	Time spent	7
Asano 2018	124	64.1 years	NM	Singapore	TSR: Tablet + CT	43 h	/	2MWT	Time spent	8
Baldwin 2018	19	59.2 years	1.7 months	Australia	NTSR + mCIMT	11.5 h	FM	Barthel	/	7
Ballester 2017	35	63.4 years	31.2 months	Spain	TSR: Virtual serious game	10 h	/	WMFT	#compliers	5
Baskett 1999	100	69.8 years	1.3 month	New Zealand	NTSR + CT	9 h	Grip strength	10mWT	Time spent	8
Burgos 2020	10	61.3 years	6.9 months	Chile	TSR: Tablet + CT	26 h	/	BBS	/	6
Chen 2016	54	66.3 years	.9 month	China	TSR: FES + CT	20 h	Muscle Contraction	BBS	/	8
Choi 2016	24	66 years	15.1 months	South Korea	TSR: Tablet + CT	10 h	FM	EQ-5D	/	6
Chumbler 2012	52	67.4 years	1.7 month	USA	TSR: Assistive device + CT	NM	/	FIM	/	8
Dettmers 2013	56	58.5 years	40.2 months	Germany	NTSR: Video instructions	42 h	/	NHPT	/	5
Emmerson 2016	62	66 years	4.5 months	Australia	NTSR: Video instructions	16 h	Grip strength	WMFT	Time spent	7
Ertekin 2009	20	62.6 years	13.7 months	Turkey	NTSR: Written instructions	156 h	/	BBS	/	6
Golla 2018	14	74 years	4.3 months	Germany	TSR: Unsupervised Wii training + CT	45 h	Stability indicator	TUG	Time spent	5
Hara 2008	20	58.3 years	13 months	Japan	TSR: FES + CT	105 h	mAS	NHPT	/	5
Harris 2009	103	69.4 years	.7 month	Canada	NTSR: Written instructions + CT	112 h	CAHAI	ARAT	Time spent	8
Hofstad 2014	306	72.2 years	<3 months	Norway	NTSR + CT	15.5 h	/	mRS	/	6
Huijgen 2008	16	69 years	36.5 months	Netherlands	TSR: Home care desk system + CT	19 h	/	ARAT	Time spent	6
Lin 2014	24	75.1 years	36.7 months	Taiwan	TSR: Virtual serious game	10 h	/	BBS	/	7
Linder 2015	99	57.5 years	4 months	USA	TSR: Unsupervised RAT + CT	120 h	SIS hand function	/	Time spent	6
Llorens 2015	30	55.5 years	10.9 months	Spain	TSR: Virtual serious game + CT	18 h	/	BBS	/	8
Malagoni 2016	20	66.5 years	79.1 months	Italy	NTSR	20 h	/	6MWT	#compliers	6
Nijenhuis 2016	20	59.5 years	16.5 months	Netherlands	TSR: Virtual serious game	18 h	FM	ARAT	Time spent	6
Olney 2006	72	64.7 years	45.6 months	Canada	NTSR: Written instructions + CT	45 h	/	6MWT	/	7
Piron 2009	36	65.2 years	13.3 months	Italy	TSR: Virtual serious game	20 h	FM	/	/	7
Pradines 2019	23	56 years	109.5 months	France	NTSR: Written instructions + CT	50 h	/	Gait speed	Time spent	6

Table 1. Characteristics of Included Trials (continued).

Authors	Participants	Age (mean)	Stroke onset (mean)	Country	Intervention	Intervention duration (mean)	Body function	Activity	Adherence	PEDro
Rand 2017	24	62 years	16.3 months	Israel	TSR: Unsupervised kinect training	30 h	/	ARAT	Time spent	8
Saywell 2021	95	73.5 years	6.7 months	New Zealand	TSR: Home care desk system	>15 h	Grip strength	EQ-5D	/	8
Standen 2016	27	61 years	5.33 months	UK	TSR: Virtual serious game	56 h	/	WMFT	/	6
Stinear 2008	32	55.3 years	24.5 months	New Zealand	TSR: Active-passive device + CT	18.5 h	FM	/	/	5
Treger 2014	56	59.4 years	2 months	Israel	NTSR	42 h	/	10 mWT	Time spent	8
Turton 2016	47	66.3 years	4.9 months	UK	NTSR + CT	42 h	/	ARAT	Time spent	7
Wolf 2015	99	56.9 years	4 months	USA	TSR: Virtual serious game + CT	120 h	FM	ARAT	Time spent	7
Zondervan 2015	16	57.5 years	29 months	USA	TSR: Resonating arm exerciser	27 h	FM	BBT	Time spent	6
Zondervan 2016	18	59.5 years	51.7 months	USA	TSR: Virtual serious game	27 h	/	ARAT	Time spent	6

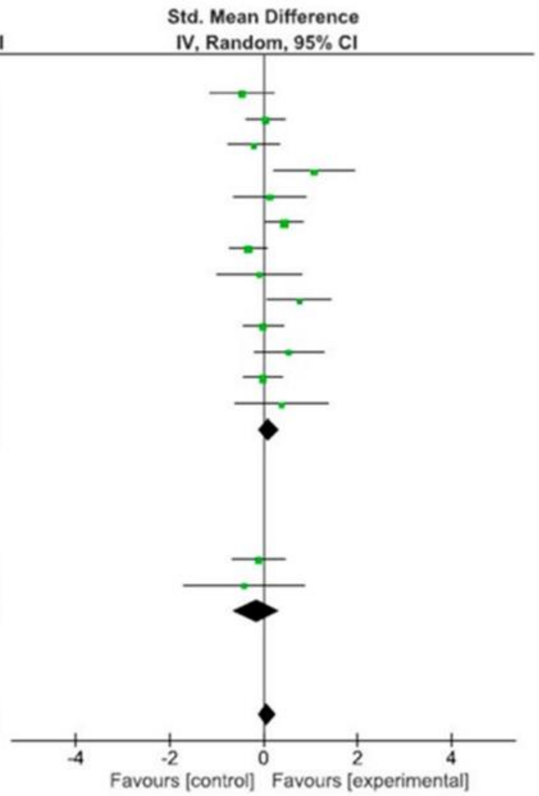
Abbreviations: UK, United Kingdom; USA, United States of America; TSR, technologically assisted self-rehabilitation; SR, non-technologically assisted self-rehabilitation; mCIMT, modified constraint induced movement therapy; FES, functional electrical stimulation; RAT, robot-assisted therapy; CT, conventional therapy; PT, passive treatment; NT, no treatment; FM, Fugl–Meyer ; mAS, modified Ashworth scale; CAHAI, Chedoke arm and hand inventory; SIS, stroke impact scale; ARAT, action research arm test; 2MWT, 2 minute walking test; WMFT, Wolf motor function test; 10mWT, 10 meter walking test; BBS, Berg Balance Scale ; FIM, functional independence measure; NHPT, Nine Hole Peg Test; TUG, Timed Up and Go Test; mRS, modified rankin scale; 6MWT, 6 minute walking test; BBT, Box and Block Test; #compliers. number of patients that completed all sessions.

Effect of Self-Rehabilitation on Motor Function

Fifteen trials (44%) measured motor function according to the first ICF component. Among these, thirteen reported quantitative outcomes; eleven regarding UL, one regarding lower limb, and one regarding full body. UL motor function assessments consisted of measuring control of voluntary movements (movement quality), muscle power (grip strength and lower limb muscular contraction), and motor reflex (spasticity) according to the ICF core sets. Outcomes of the intervention group improved in 12 trials (92%) and all trials showed an improvement in the control group. As presented in Figure 2, self-rehabilitation showed similar effectiveness to conventional therapy for motor function recovery (SMD = .09; 95% CI = .11 to .28; P = .39). Subgroup analysis (P = .34) revealed that UL self-rehabilitation (SMD = .12; 95% CI = .1 to .33; P = .29) and lower limb self-rehabilitation (SMD = .15; 95% CI = .66 to .36; P = .56) were similarly effective. The Grade Approach disclosed a low certainty of evidence regarding self-rehabilitation effect on motor function (Supplementary Material 5) related to the fact that few studies assessed motor function and that heterogeneity between results was moderate (I^2 = 40%). The effect size quantified by the SMD was considered as low [186].

Figure 2. Self-rehabilitation effect on motor function for upper and lower limb represented through a forest plot.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 Upper-limb								
Ballester et al., 2017	-0.18	3.05	17	1.39	3.63	18	5.8%	-0.46 [-1.13, 0.22]
Baskett et al., 1999	4.1	7.1	42	3.8	5.5	46	10.0%	0.05 [-0.37, 0.47]
Chen et al., 2016	37.08	13.404	26	39.58	10.351	24	7.4%	-0.20 [-0.76, 0.35]
Choi et al., 2016	29.25	13.908	12	13.17	14.879	12	4.0%	1.08 [0.21, 1.94]
Emmerson et al., 2016	1.4	2.5	13	0.9	4.5	13	4.8%	0.13 [-0.64, 0.90]
Harris et al., 2009	14.2	13.104	53	7.9	14.989	50	10.6%	0.45 [0.05, 0.84]
Linder et al., 2015	22.7	11.55	51	26.5	11.63	48	10.4%	-0.33 [-0.72, 0.07]
Nijenhuis et al., 2016	0.17	19.612	9	1.67	14.373	10	3.8%	-0.08 [-0.99, 0.82]
Piron et al., 2009	4.8	4.586	18	1.5	3.809	18	5.7%	0.77 [0.09, 1.45]
Saywell et al., 2021	1.2	7.446	39	1.3	8.779	44	9.7%	-0.01 [-0.44, 0.42]
Stinear et al., 2008	27.1	29.274	18	10.8	29.445	12	5.0%	0.54 [-0.20, 1.29]
Wolf et al., 2015	9.3	11.203	47	9.567	11.073	45	10.2%	-0.02 [-0.43, 0.39]
Zondervan et al., 2015	2.88	4.68	8	1.31	2.59	8	3.2%	0.39 [-0.60, 1.38]
Subtotal (95% CI)			**353**			**348**	**90.5%**	**0.12 [-0.10, 0.33]**
Heterogeneity: Tau² = 0.07; Chi² = 22.23, df = 12 (P = 0.03); I² = 46%								
Test for overall effect: Z = 1.06 (P = 0.29)								
2.1.2 Lower-Limb								
Chen et al., 2016	58.62	22.632	26	60.73	17.177	24	7.4%	-0.10 [-0.66, 0.45]
Golla et al., 2018	2.775	5.424	4	6.67	9.708	6	2.1%	-0.42 [-1.71, 0.87]
Subtotal (95% CI)			**30**			**30**	**9.5%**	**-0.15 [-0.66, 0.36]**
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%								
Test for overall effect: Z = 0.59 (P = 0.56)								
Total (95% CI)			**383**			**378**	**100.0%**	**0.09 [-0.11, 0.28]**
Heterogeneity: Tau² = 0.05; Chi² = 23.20, df = 14 (P = 0.06); I² = 40%								
Test for overall effect: Z = 0.86 (P = 0.39)								
Test for subgroup differences: Chi² = 0.91, df = 1 (P = 0.34), I² = 0%								



Effect of Self-Rehabilitation on Activity

Thirty-one trials measured activity according to the second ICF component. Among these, twenty-six reported quantitative outcomes. Selected outcomes were assessed according to the ICF set scores for hand and arm use (reaching and grasping), walking (gait speed and balance), and mobility. Funnel plot graphic representation revealed asymmetry and the presence of one outlier [225]. Sensitivity analysis after removal of the outlier showed no significant difference (Supplementary Material 6). From the remaining trials, twenty-four (96%) showed an improvement in the intervention group and twenty-one (88%) in the control group. Meta-analysis showed that self-rehabilitation was as effective as conventional therapy to improve activity outcomes (SMD = .08; 95% CI = .04 to .19; P = .18) (Figure 3). Subgroup analysis (P = .23) showed no superiority of self-rehabilitation using technological devices (SMD = .01; 95% CI = .14 to .16; P = .88) compared to self-rehabilitation not using technology (SMD = .15; 95% CI = .01 to .31; P = .07). Self-rehabilitation appeared equally effective when delivered in addition to (SMD = .06; 95% CI = .07 to .19; P = .36) or in substitution of (SMD = .11; 95% CI = .09 to .31; P = .29) conventional therapy (Figure 4), irrespective of whether patients were in the subacute (SMD = .07; 95% CI = .06 to .20; P = .27) or chronic stages (SMD = .09; 95% CI = .14 to .31; P = .44) (Figure 5), and for programs of different duration (SMD = .12; 95% CI = .00 to .24; P = .06) (Figure 6). Sensitivity analysis revealed no significant difference between upper and lower limb self-rehabilitation on activity (Figure 7). Influence of trial location was also found to be non-significant (P = .94) (Supplementary Material 7). The certainty of evidence regarding the self-rehabilitation effect on activity was qualified as moderate according to the Grade Approach (Supplementary Material 8). Inconsistency, indirectness, and risk of bias were judged to be low for all subgroup analyses. In addition, heterogeneity between studies was found to be non-significant (I^2 = 0%). The effect size quantified by the SMD was considered as low [238].

Adherence to Self-Rehabilitation

Eighteen trials reported measures related to treatment adherence. Six trials showed that patients spent the same or more time performing exercises in the intervention than control groups. However, seven trials showed that patients from the intervention group spent less time performing exercises than patients from the control group. Five trials reported that 15 to 40% of patients did not reach the total amount of sessions.

Seventeen RCT (50%) explicitly revealed providing real time sessions, eighteen (53%) used sensing platforms, nine (26%) supplied performance visual feedback, seven (20%) defined clearly measurable objectives, and twenty-two (65%) gave written or video-registered instructions.

Figure 3. Technologically assisted and non-technologically assisted self-rehabilitation effect on activity represented through a forest plot.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Technologically-assisted self-rehabilitation								
Adie et al., 2016	8.3	9.601	99	8.3	10.002	101	15.9%	0.00 [-0.28, 0.28]
Ballester et al., 2017	-3.3	8.09	17	-0.11	3.98	18	2.7%	-0.49 [-1.17, 0.18]
Burgos et al., 2020	11.33	2.709	6	7	6.891	4	0.7%	0.83 [-0.52, 2.17]
Chen et al., 2016	7.35	2.565	26	7.76	3.602	24	4.0%	-0.13 [-0.69, 0.43]
Chumbler et al., 2012	0.2	6.147	24	0.6	7.622	19	3.4%	-0.06 [-0.66, 0.54]
Golla et al., 2018	1.3	0.895	4	1.13	2.952	6	0.8%	0.06 [-1.20, 1.33]
Huijgen et al., 2008	0.2	8.257	9	0.6	32.639	3	0.7%	-0.02 [-1.33, 1.28]
Lin et al., 2014	4.2	3.248	11	4.5	3.322	12	1.8%	-0.09 [-0.91, 0.73]
Llorens et al., 2015	4	2.521	15	2.47	3.205	15	2.3%	0.52 [-0.21, 1.25]
Nijenhuis et al., 2016	0.33	22.622	9	2.06	13.967	10	1.5%	-0.09 [-0.99, 0.81]
Rand et al., 2017	11.7	11.417	11	9	12.606	10	1.7%	0.22 [-0.64, 1.08]
Saywell et al., 2021	6.3	11.323	38	2.1	15.444	41	6.2%	0.31 [-0.14, 0.75]
Standen et al., 2016	3.17	7.975	9	1.17	3.688	9	1.4%	0.31 [-0.62, 1.24]
Wolf et al., 2015	5.13	9.932	47	8.8	10.319	45	7.2%	-0.36 [-0.77, 0.05]
Zondervan et al., 2015	1.88	4.22	8	0.63	1.19	8	1.2%	0.38 [-0.61, 1.37]
Zondervan et al., 2016	0.7	2.3	9	-0.6	2.9	8	1.3%	0.48 [-0.49, 1.44]
Subtotal (95% CI)			**342**			**333**	**52.8%**	**0.01 [-0.14, 0.16]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 12.63$, df = 15 (P = 0.63); $I^2 = 0\%$								
Test for overall effect: Z = 0.15 (P = 0.88)								
1.1.2 Non-technologically-assisted self-rehabilitation								
Baldwin et al., 2018	0.3	0.506	10	0.6	0.361	6	1.1%	-0.62 [-1.66, 0.42]
Baskett et al., 1999	3.7	10.8	43	3.6	5.7	43	6.9%	0.01 [-0.41, 0.43]
Emmerson et al., 2016	8	13	28	4	13	30	4.6%	0.30 [-0.21, 0.82]
Ertekin et al., 2009	19.6	6.2	10	22.6	9.4	10	1.6%	-0.36 [-1.25, 0.52]
Harris et al., 2009	11.73	15.445	53	7.3	16.211	50	8.1%	0.28 [-0.11, 0.67]
Hofstad et al., 2014	0.13	0.87	104	-0.07	0.912	99	16.1%	0.22 [-0.05, 0.50]
Malagoni et al., 2016	48.7	73.349	6	50.7	76.477	6	1.0%	-0.02 [-1.16, 1.11]
Pradines et al., 2019	0.11	0.095	8	0.04	0.19	8	1.2%	0.44 [-0.56, 1.44]
Treger et al., 2014	3.64	8.12	28	1.07	12.527	25	4.2%	0.24 [-0.30, 0.78]
Turton et al., 2016	2.84	10.244	16	5.33	7.594	16	2.5%	-0.27 [-0.97, 0.43]
Subtotal (95% CI)			**306**			**293**	**47.2%**	**0.15 [-0.01, 0.31]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.72$, df = 9 (P = 0.67); $I^2 = 0\%$								
Test for overall effect: Z = 1.78 (P = 0.07)								
Total (95% CI)			**648**			**626**	**100.0%**	**0.08 [-0.04, 0.19]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 20.77$, df = 25 (P = 0.71); $I^2 = 0\%$								
Test for overall effect: Z = 1.34 (P = 0.18)								
Test for subgroup differences: $Chi^2 = 1.41$, df = 1 (P = 0.23), $I^2 = 29.2\%$								

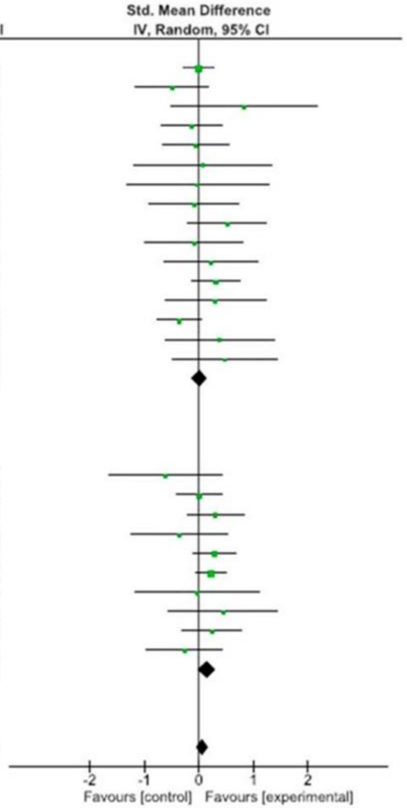


Figure 4. Effect of self-rehabilitation in addition or substitution to conventional therapy on activity represented through a forest plot.

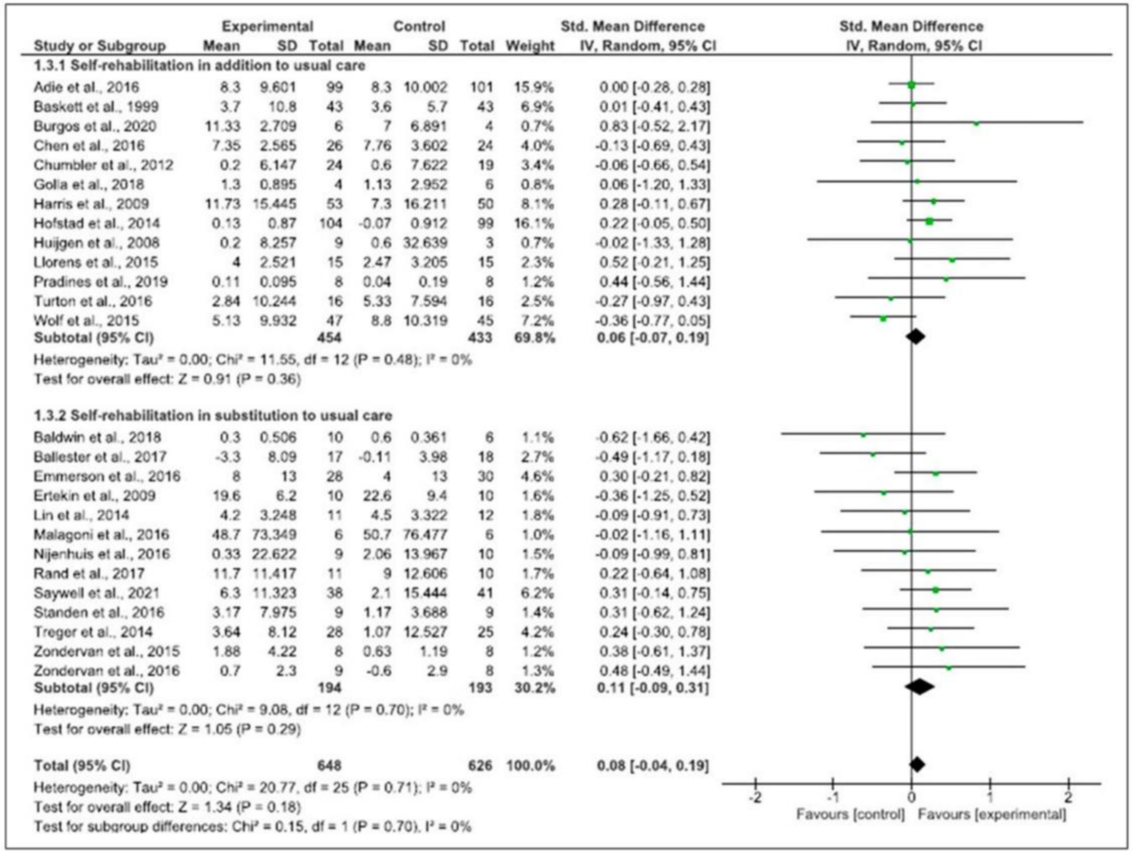


Figure 5. Effect of self-rehabilitation on acute vs chronic patients with stroke on activity represented through a forest plot.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.7.1 Acute/Subacute								
Adie et al., 2016	8.3	9.601	99	8.3	10.002	101	15.9%	0.00 [-0.28, 0.28]
Baskett et al., 1999	3.7	10.8	43	3.6	5.7	43	6.9%	0.01 [-0.41, 0.43]
Burgos et al., 2020	11.33	2.709	6	7	6.891	4	0.7%	0.83 [-0.52, 2.17]
Chen et al., 2016	7.35	2.565	26	7.76	3.602	24	4.0%	-0.13 [-0.69, 0.43]
Chumbler et al., 2012	0.2	6.147	24	0.6	7.622	19	3.4%	-0.06 [-0.66, 0.54]
Emmerson et al., 2016	8	13	28	4	13	30	4.6%	0.30 [-0.21, 0.82]
Golla et al., 2018	1.3	0.895	4	1.13	2.952	6	0.8%	0.06 [-1.20, 1.33]
Harris et al., 2009	11.73	15.445	53	7.3	16.211	50	8.1%	0.28 [-0.11, 0.67]
Hofstad et al., 2014	0.13	0.87	104	-0.07	0.912	99	16.1%	0.22 [-0.05, 0.50]
Standen et al., 2016	3.17	7.975	9	1.17	3.688	9	1.4%	0.31 [-0.62, 1.24]
Treger et al., 2014	3.64	8.12	28	1.07	12.527	25	4.2%	0.24 [-0.30, 0.78]
Turton et al., 2016	2.84	10.244	16	5.33	7.594	16	2.5%	-0.27 [-0.97, 0.43]
Wolf et al., 2015	5.13	9.932	47	8.8	10.319	45	7.2%	-0.36 [-0.77, 0.05]
Subtotal (95% CI)			**487**			**471**	**75.7%**	**0.07 [-0.06, 0.20]**
Heterogeneity: Tau² = 0.00; Chi² = 10.99, df = 12 (P = 0.53); I² = 0%								
Test for overall effect: Z = 1.10 (P = 0.27)								
1.7.2 Chronic								
Baldwin et al., 2018	0.3	0.506	10	0.6	0.361	6	1.1%	-0.62 [-1.66, 0.42]
Ballester et al., 2017	-3.3	8.09	17	-0.11	3.98	18	2.7%	-0.49 [-1.17, 0.18]
Ertekin et al., 2009	19.6	6.2	10	22.6	9.4	10	1.6%	-0.36 [-1.25, 0.52]
Huijgen et al., 2008	0.2	8.257	9	0.6	32.639	3	0.7%	-0.02 [-1.33, 1.28]
Lin et al., 2014	4.2	3.248	11	4.5	3.322	12	1.8%	-0.09 [-0.91, 0.73]
Llorens et al., 2015	4	2.521	15	2.47	3.205	15	2.3%	0.52 [-0.21, 1.25]
Malagoni et al., 2016	48.7	73.349	6	50.7	76.477	6	1.0%	-0.02 [-1.16, 1.11]
Nijenhuis et al., 2016	0.33	22.622	9	2.06	13.967	10	1.5%	-0.09 [-0.99, 0.81]
Pradines et al., 2019	0.11	0.095	8	0.04	0.19	8	1.2%	0.44 [-0.56, 1.44]
Rand et al., 2017	11.7	11.417	11	9	12.606	10	1.7%	0.22 [-0.64, 1.08]
Saywell et al., 2021	6.3	11.323	38	2.1	15.444	41	6.2%	0.31 [-0.14, 0.75]
Zondervan et al., 2015	1.88	4.22	8	0.63	1.19	8	1.2%	0.38 [-0.61, 1.37]
Zondervan et al., 2016	0.7	2.3	9	-0.6	2.9	8	1.3%	0.48 [-0.49, 1.44]
Subtotal (95% CI)			**161**			**155**	**24.3%**	**0.09 [-0.14, 0.31]**
Heterogeneity: Tau² = 0.00; Chi² = 9.76, df = 12 (P = 0.64); I² = 0%								
Test for overall effect: Z = 0.77 (P = 0.44)								
Total (95% CI)			**648**			**626**	**100.0%**	**0.08 [-0.04, 0.19]**
Heterogeneity: Tau² = 0.00; Chi² = 20.77, df = 25 (P = 0.71); I² = 0%								
Test for overall effect: Z = 1.34 (P = 0.18)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%								

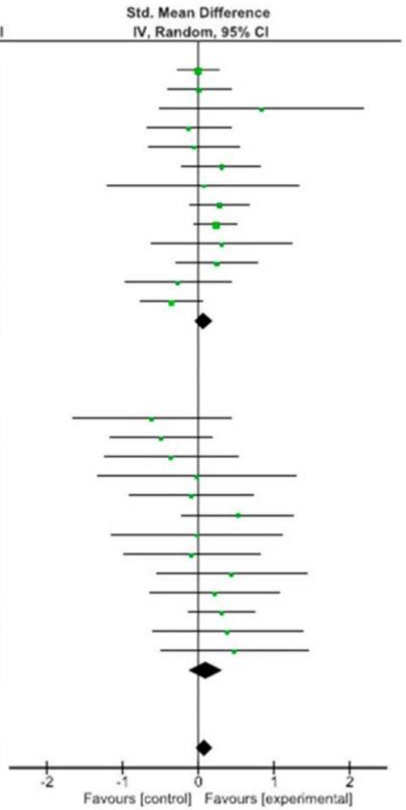
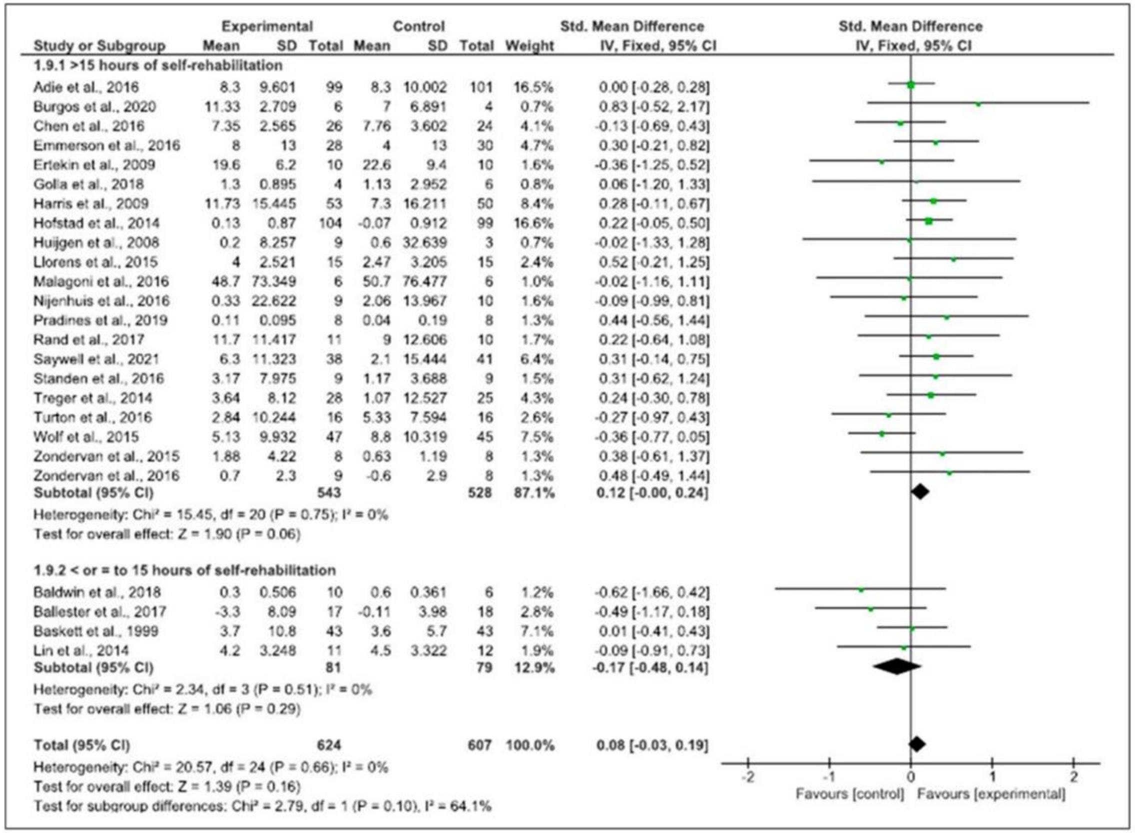


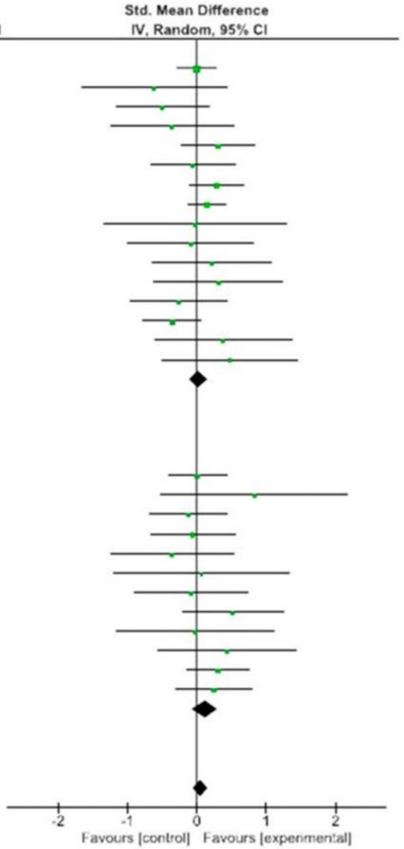
Figure 6. Effect of total duration of self-rehabilitation programs on activity represented through a forest plot.



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.9.1 >15 hours of self-rehabilitation								
Adie et al., 2016	8.3	9.601	99	8.3	10.002	101	16.5%	0.00 [-0.28, 0.28]
Burgos et al., 2020	11.33	2.709	6	7	6.891	4	0.7%	0.83 [-0.52, 2.17]
Chen et al., 2016	7.35	2.565	26	7.76	3.602	24	4.1%	-0.13 [-0.69, 0.43]
Emmerson et al., 2016	8	13	28	4	13	30	4.7%	0.30 [-0.21, 0.82]
Ertekin et al., 2009	19.6	6.2	10	22.6	9.4	10	1.6%	-0.36 [-1.25, 0.52]
Golla et al., 2018	1.3	0.895	4	1.13	2.952	6	0.8%	0.06 [-1.20, 1.33]
Harris et al., 2009	11.73	15.445	53	7.3	16.211	50	8.4%	0.28 [-0.11, 0.67]
Hofstad et al., 2014	0.13	0.87	104	-0.07	0.912	99	16.6%	0.22 [-0.05, 0.50]
Huijgen et al., 2008	0.2	8.257	9	0.6	32.639	3	0.7%	-0.02 [-1.33, 1.28]
Llorens et al., 2015	4	2.521	15	2.47	3.205	15	2.4%	0.52 [-0.21, 1.25]
Malagoni et al., 2016	48.7	73.349	6	50.7	76.477	6	1.0%	-0.02 [-1.16, 1.11]
Nijenhuis et al., 2016	0.33	22.622	9	2.06	13.967	10	1.6%	-0.09 [-0.99, 0.81]
Pradines et al., 2019	0.11	0.095	8	0.04	0.19	8	1.3%	0.44 [-0.56, 1.44]
Rand et al., 2017	11.7	11.417	11	9	12.606	10	1.7%	0.22 [-0.64, 1.08]
Saywell et al., 2021	6.3	11.323	38	2.1	15.444	41	6.4%	0.31 [-0.14, 0.75]
Standen et al., 2016	3.17	7.975	9	1.17	3.688	9	1.5%	0.31 [-0.62, 1.24]
Treger et al., 2014	3.64	8.12	28	1.07	12.527	25	4.3%	0.24 [-0.30, 0.78]
Turton et al., 2016	2.84	10.244	16	5.33	7.594	16	2.6%	-0.27 [-0.97, 0.43]
Wolf et al., 2015	5.13	9.932	47	8.8	10.319	45	7.5%	-0.36 [-0.77, 0.05]
Zondervan et al., 2015	1.88	4.22	8	0.63	1.19	8	1.3%	0.38 [-0.61, 1.37]
Zondervan et al., 2016	0.7	2.3	9	-0.6	2.9	8	1.3%	0.48 [-0.49, 1.44]
Subtotal (95% CI)			**543**			**528**	**87.1%**	**0.12 [-0.00, 0.24]**
Heterogeneity: $Chi^2 = 15.45$, df = 20 (P = 0.75); $I^2 = 0\%$								
Test for overall effect: Z = 1.90 (P = 0.06)								
1.9.2 < or = to 15 hours of self-rehabilitation								
Baldwin et al., 2018	0.3	0.506	10	0.6	0.361	6	1.2%	-0.62 [-1.66, 0.42]
Ballester et al., 2017	-3.3	8.09	17	-0.11	3.98	18	2.8%	-0.49 [-1.17, 0.18]
Baskett et al., 1999	3.7	10.8	43	3.6	5.7	43	7.1%	0.01 [-0.41, 0.43]
Lin et al., 2014	4.2	3.248	11	4.5	3.322	12	1.9%	-0.09 [-0.91, 0.73]
Subtotal (95% CI)			**81**			**79**	**12.9%**	**-0.17 [-0.48, 0.14]**
Heterogeneity: $Chi^2 = 2.34$, df = 3 (P = 0.51); $I^2 = 0\%$								
Test for overall effect: Z = 1.06 (P = 0.29)								
Total (95% CI)			**624**			**607**	**100.0%**	**0.08 [-0.03, 0.19]**
Heterogeneity: $Chi^2 = 20.57$, df = 24 (P = 0.66); $I^2 = 0\%$								
Test for overall effect: Z = 1.39 (P = 0.16)								
Test for subgroup differences: $Chi^2 = 2.79$, df = 1 (P = 0.10), $I^2 = 64.1\%$								

Figure 7. Self-rehabilitation effect on activity for upper and lower limb represented through a forest plot.

	Experimental			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
1.12.1 Upper-limb								
Adie et al., 2016	8.3	9.601	99	8.3	10.002	101	15.2%	0.00 [-0.28, 0.28]
Baldwin et al., 2018	0.3	0.506	10	0.6	0.361	6	1.1%	-0.62 [-1.66, 0.42]
Ballester et al., 2017	-3.3	8.09	17	-0.11	3.98	18	2.6%	-0.49 [-1.17, 0.18]
Chumbler et al., 2012	19.6	6.2	10	22.6	9.4	10	1.5%	-0.36 [-1.25, 0.52]
Emmerson et al., 2016	8	13	28	4	13	30	4.3%	0.30 [-0.21, 0.82]
Ertekin et al., 2009	0.2	6.147	24	0.6	7.622	19	3.2%	-0.06 [-0.66, 0.54]
Harris et al., 2009	11.73	15.445	53	7.3	16.211	50	7.7%	0.28 [-0.11, 0.67]
Hofstad et al., 2014	0.13	0.87	104	0	0.912	99	15.4%	0.15 [-0.13, 0.42]
Huijgen et al., 2008	0.2	8.257	9	0.6	32.639	3	0.7%	-0.02 [-1.33, 1.28]
Nijenhuis et al., 2016	0.33	22.622	9	2.06	13.967	10	1.4%	-0.09 [-0.99, 0.81]
Rand et al., 2017	11.7	11.417	11	9	12.606	10	1.6%	0.22 [-0.64, 1.08]
Standen et al., 2016	3.17	7.975	9	1.17	3.688	9	1.3%	0.31 [-0.62, 1.24]
Turton et al., 2016	2.84	10.244	16	5.33	7.594	16	2.4%	-0.27 [-0.97, 0.43]
Wolf et al., 2015	5.13	9.932	47	8.8	10.319	45	6.9%	-0.36 [-0.77, 0.05]
Zondervan et al., 2015	1.88	4.22	8	0.63	1.19	8	1.2%	0.38 [-0.61, 1.37]
Zondervan et al., 2016	0.7	2.3	9	-0.6	2.9	8	1.2%	0.48 [-0.49, 1.44]
Subtotal (95% CI)			**463**			**442**	**67.7%**	**0.02 [-0.11, 0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 14.00, df = 15 (P = 0.53); I² = 0%								
Test for overall effect: Z = 0.35 (P = 0.73)								
1.12.2 Lower-limb								
Baskett et al., 1999	3.7	10.8	43	3.6	5.7	43	6.5%	0.01 [-0.41, 0.43]
Burgos et al., 2020	11.33	2.709	6	7	6.891	4	0.6%	0.83 [-0.52, 2.17]
Chen et al., 2016	7.35	2.565	26	7.76	3.602	24	3.8%	-0.13 [-0.69, 0.43]
Chumbler et al., 2012	0.2	6.147	24	0.6	7.622	19	3.2%	-0.06 [-0.66, 0.54]
Ertekin et al., 2009	19.6	6.2	10	22.6	9.4	10	1.5%	-0.36 [-1.25, 0.52]
Golla et al., 2018	1.3	0.895	4	1.13	2.952	6	0.7%	0.06 [-1.20, 1.33]
Lin et al., 2014	4.2	3.248	11	4.5	3.322	12	1.7%	-0.09 [-0.91, 0.73]
Llorens et al., 2015	4	2.521	15	2.47	3.205	15	2.2%	0.52 [-0.21, 1.25]
Malagoni et al., 2016	48.7	73.349	6	50.7	76.477	6	0.9%	-0.02 [-1.16, 1.11]
Pradines et al., 2019	0.11	0.095	8	0.04	0.19	8	1.2%	0.44 [-0.56, 1.44]
Saywell et al., 2021	6.3	11.323	38	2.1	15.444	41	5.9%	0.31 [-0.14, 0.75]
Treger et al., 2014	3.64	8.12	28	1.07	12.527	25	4.0%	0.24 [-0.30, 0.78]
Subtotal (95% CI)			**219**			**213**	**32.3%**	**0.11 [-0.08, 0.30]**
Heterogeneity: Tau² = 0.00; Chi² = 6.27, df = 11 (P = 0.85); I² = 0%								
Test for overall effect: Z = 1.18 (P = 0.24)								
Total (95% CI)			**682**			**655**	**100.0%**	**0.05 [-0.06, 0.16]**
Heterogeneity: Tau² = 0.00; Chi² = 20.86, df = 27 (P = 0.79); I² = 0%								
Test for overall effect: Z = 0.96 (P = 0.34)								
Test for subgroup differences: Chi² = 0.59, df = 1 (P = 0.44), I² = 0%								



4.5 Discussion

The present meta-analysis showed low to moderate certainty of evidence that self-rehabilitation efficacy was equally effective to conventional therapy for post-stroke motor function and activity. Most of the included RCTs reported improvements in both intervention and control groups for lower and UL outcomes. Subgroup analyses revealed that trial location, use of technology, intervention design, dose and stroke stage classification were all statistically nonsignificant. The results of this meta-analysis are globally in line with previous reviews that assessed self-rehabilitation [193] or telerehabilitation [198-201, 239, 240] effects on motor function or activity of adults after stroke. In 2018, Da Silva et al., conducted a meta-analysis to assess self-rehabilitation efficacy on post-stroke arm function [193]. Results revealed that constrained-induced movement therapy, electrical stimulation, and non-technological programs were superior to other technological self-rehabilitation programs. Treatment dose and stroke stage were shown to significantly influence poststroke motor outcomes. However, some of these findings differed from our results. This might be explained by the fact that the review of Da Silva et al., only focused on arm rehabilitation and included non–RCTs (50% studies) and with a high risk of bias.

The 2019 meta-analysis of Rintala et al. [200] compared telerehabilitation to other programs that could improve physical functioning after stroke. Results showed that online video monitoring programs, telephone interventions, and DVD exercises were equally effective for daily living activity outcomes. A recent Cochrane review suggested that telerehabilitation could not be considered as inferior to conventional therapy to improve balance, UL function, and daily living activity [198]. Two other meta-analyses showed similar results on both upper and lower limb motor function activity, and participation [199, 201]. However, none of these papers focused on non-technological interventions.

Parameters That Influence Self-Rehabilitation Effect on Activity

This review showed that technologically assisted compared to non-technologically assisted self-rehabilitation had equal effects on motor function outcome measures relative to control conditions. This neutral finding may be explained by the use of new-technologies on post-stroke outcomes having heterogeneous effects that differ between the types of technologies such as virtual reality vs robot-assisted therapy and the specific methods of each therapy (e.g., immersive vs computer screen virtual reality) [24, 59]. For example, a recent meta-analysis showed that virtual reality and serious game implementation led to superior outcomes compared to conventional therapy when provided in hospital [61]. Similarly, another systematic review with meta-analysis revealed that the outcomes of robot-assisted therapy were superior to any other therapy [24]. However, these results are not supported by a recent RCT that did not show significant effects of robot-assisted therapy on UL motor function and activity when compared to conventional therapy of the same frequency and duration [41]. For comparison between the present paper and the first two papers reporting superior effects of technology use on outcomes, the absence of supervision from a therapist when patients were self-rehabilitated with technological devices may have decreased outcome performance making self-rehabilitation equally valuable to conventional therapy made with a therapist. The differences between the three papers and the present paper also may reflect subtle differences in using different types of technologies and differences in the user-friendly interface design of the technology. Irrespective of whether or not technology enhances rehabilitation relative to conventional therapy, the results of the present paper lend support to the use of technologically assisted self-rehabilitation for prolongation of effective treatment following hospital-based rehabilitation.

Certain trials included in this review reported a lack of adherence to self-rehabilitation programs. Poor treatment adherence may be responsible for non-significant outcomes in rehabilitation. In their article of 2018, Argent et al. [204] identified several factors that may influence adherence to self-rehabilitation. Psychological and cognitive factors have been highlighted as potential reasons for reduced treatment compliance. External locus of control, feeling pain during exercises, having a low level of physical activity, and not being supported by family or friends were also reported as contributors to bad treatment adherence. In the same review, the authors suggested a few solutions to consider in order to improve treatment compliance. First, by providing real time sessions (face-to-face or by video conference) and with sensing platforms such as cameras or inertial measurement units that measure activity during the patient's home exercises. These measures provide the clinician with a better understanding of the patient's behaviour and problems, and they would therefore be able to give feedbacks and adapt the program to an appropriate level of difficulty for the patient, thereby maintaining treatment compliance. Second, the identification of clear measurable objectives and the implementation of visual feedback (such as graphics) on patient's weekly performance (e.g., level of physical activity and time spent in rehabilitation) were considered as parameters moderating treatment adherence. Lastly, patient's education on their pathology and the provision of written operating instructions on the exercises to perform improved intervention compliance.

Our meta-analysis suggests that self-rehabilitation can be performed in addition to or in substitution of conventional therapy, in adults with subacute and chronic stroke. These results are not in line with the meta-analysis of Da Silva et al., 2018, since the authors showed that self-rehabilitation had a superior effect for arm recovery when performed in patients more than 12 months post-stroke compared to more recent time since stroke onset [193]. This could be explained by the fact that our review assessed different outcomes at different times after stroke.

Cost-Effectiveness of Self-Rehabilitation

Self-rehabilitation may be far less expensive than conventional therapy in terms of time saved for the patient, care partner or clinician. In this review, only four studies evaluated the cost of intervention [89, 189, 232, 235]. Among these, one study performed a cost-effectiveness analysis and showed that its program was more cost-effective than conventional face-to-face therapy [189]. This finding is supported by previous work that conducted cost-effectiveness analysis to compare telerehabilitation programs to conventional therapy in other pathologies [241].

Implications for Clinical Practice

Our results indicate with a low to moderate body of consistent evidence that self-rehabilitation of motor function and activity is equal to conventional therapy. Self-rehabilitation should be considered as an additional method allowing to increase rehabilitation intensity or duration. The rehabilitation team could implement the rehabilitation plan depending on the patient's functional assessment, delay since stroke, and contextual factors. Self-rehabilitation is thus complementary to face-to-face practice and should not replace it. Indeed, by providing self-rehabilitation in addition to conventional therapy, the burden of healthcare professionals will be reduced and facilitated. Furthermore, self-rehabilitation may help to increase therapy time and offer treatment for patients who may not otherwise have a treatment opportunity, whatever the delay since stroke. A recent RCT conducted in Benin showed great potential to provide such programs in developing countries [242]. Lastly, the COVID-19 crisis has imposed new constraints to both therapists and patients [243]. For both these scenarios, developing the means to provide self-rehabilitation (whether supplied with technological devices or not) must be considered to increase treatment opportunities as a potential solution when access to treatment is reduced. Regarding the content of self-rehabilitation, future programs should use new low-cost technologies (such as smartwatches, tablets, smartphones, and virtual reality) to improve and assess adherence to treatment. The content of these structured programs should be designed by a rehabilitation professional defining agreed objectives with the patient, giving clear instructions (written or video), and providing coaching during real time sessions. The content should be based on intense physical exercises that are progressively adapted in difficulty, promoting use of the affected limb and providing feedback [183].

Recommendations for Future Research

There is a need for future research to precisely define the content (in terms of duration and intensity) of all group interventions and to select appropriate and recommended outcomes [89]. To this end, future trials should measure the duration and intensity of activity during self-rehabilitation and conventional therapy using objective measures. We recommend the use of actimetry measures of heart rate, smartwatches, and armbands that measure activity during rehabilitation [244]. It is also recommended to analyze movement kinematics with inertial sensors or cameras in order to objectively measure and better understand patient activity and recovery. Adherence and cost-effectiveness should also more often be assessed to better understand their impact on self-rehabilitation. Moreover, patient’s recruitment should be improved by assessing inter-subject differences and providing concealed allocation [87]. Future RCTs should also compare self-rehabilitation to the best evidence synthesis and match the dose and duration of intervention in all groups. Lastly, self-rehabilitation programs should be defined based on prognostic factors and tailored according to patient’s objectives [245].

Strengths and Limitations

This meta-analysis brings new information regarding the effects of self-rehabilitation on motor function and activity in adults with stroke according to the ICF-WHO framework. Further, this review conducted innovatory subgroup analyses to test the influence of location, stroke stage classification, type of treatment and dose, design and duration on the self-rehabilitation effect. Only RCTs of good methodological quality (PEDro score ≥5) were selected. However, some limitations must be mentioned. First, the definition of self-rehabilitation and its differentiation from conventional therapy may be subjective and difficult to quantify. Furthermore, there is no consensus on the definition of self-rehabilitation and relative to other commonly used terms such as telerehabilitation, self-directed therapy, and home-based rehabilitation. Second, although hand-searching was conducted with PEDro and Google scholar databases in order to avoid publication bias, some unpublished RCTs available in the Grey Literature may have been missed. In addition, publication biases were only assessed visually using funnel plot symmetry. No statistic indicators were considered to exclude trials responsible for the funnel plot asymmetry. Third, the limited available data regarding outcomes such as the Functional Independence Measure and the Barthel Index prevents to review the effect of self-rehabilitation on activity of daily living. Lastly, some RCTs of good quality may have not been included in the review due to unclear methodology or unpublished data.

4.6 Conclusion

This systematic review and meta-analysis provide low to moderate quality of evidence that self-rehabilitation and conventional therapy are equally effective for post-stroke motor recovery and activity. The use of technology, the total duration, and design of the intervention (self-rehabilitation in addition to vs in substitution of conventional therapy), the treated stroke population and the location of the trial did not have any influence on outcomes.

CHAPTER V – Wearable powered exoskeletons for gait training in tetraplegia: a systematic review on feasibility, safety and potential health benefits

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Published in Acta Neurologica Belgica 2022;122(5):1149-1162

doi:10.1007/s13760-022-02011-1

5.1 Abstract

Background: Recent developments in WPE allow gait training for patients after SCI. Two recent meta-analyses on gait training using WPE showed promising results for paraplegic patients. To this date, there is no review focusing on tetraplegic patients.

Objectives: The main objective of this review was to assess feasibility and safety of gait training using WPE in patients after tetraplegia.

Method: This systematic review was performed according to PRISMA-S guidelines. Two independent reviewers searched several databases for studies on gait training using WPE for tetraplegic patients. Primary outcomes concerned the number, type and severity of reported adverse events. Secondary outcomes examined potential additional health benefits.

Results: Forty-one studies (6 randomized trials, 24 cohorts and 11 cases series) were selected, including 166 tetraplegic patients, 26 with complete lesions (AIS A) and 71 with level of injury above C6. Minor adverse events were reported in 17 tetraplegic patients, concerning cutaneous, cardiovascular or musculoskeletal systems. Occurrence of adverse events is significantly higher in a paraplegic patient population compared to tetraplegic patients (p-value = 0.001). Only one major adverse event concerned a tetraplegic patient. Studies of low level of evidence suggest that gait training using WPE could lead to improvements in walking parameters, cardiovascular efficiency and to a reduction of spasticity.

Discussion & conclusion: gait training using WPE is a feasible and safe intervention for tetraplegic patients. To minimize occurrence of adverse events, a good patient selection and preparation is proposed. Future clinical trials should be performed to confirm current trends in terms of efficacy and potential additional health benefits.

Keywords: Spinal cord injury, tetraplegia, gait rehabilitation, wearable powered exoskeleton.

5.2 Background

Annual worldwide incidence of SCI is estimated between 40 and 80 people per million [3]. Among them, approximately 50% of survivors present with tetraplegia and 15% have a C4 or above neurological level of injury (NLI) [3, 246]. One-year post-SCI, up to 40% of patients with SCI achieve independent, indoor, walking ability among which only 18% without an assistive device [246]. Traditionally, severity of neurological impairments and ambulation ability determine gait training modalities after SCI [247]. During therapist-assisted gait training (TAGT), most patients require two or more therapists to support and guide lower limbs during overground or treadmill training [248]. Rehabilitation programs exclusively using TAGT have demonstrated limited efficacy with only 1% of patients reaching full recovery [246].

In recent years, new technology-based rehabilitation therapies have emerged such as RAGT with BWSS and WPE. In this review we defined WPE as computer guided systems using motorized orthoses to facilitate autonomous over ground movement in people with disabilities. Activation of these systems can be triggered by patients' voluntary movements or by a computer algorithm depending on the patients' capabilities and the exoskeleton characteristics [249-251]. WPE differ from other RAGT systems in terms of the following aspects and consequently offer new possibilities in gait rehabilitation. First, WPE allow self-balancing, overground, gait training, with or without UL assistance. Second, assistance during gait can be triggered voluntarily by the participant through muscle contraction and body movements [252, 253]. Third, gait training, through task specific rehabilitation, can be performed in more ecological environments, promoting a more human-like gait pattern (including activation of trunk muscles during over ground or treadmill training) [251, 254]. Finally, WPE enable walking with a lower energetic cost compared to other systems [251, 254].

Nowadays, Food and Drugs Administration has authorized the use of WPE in walking programs for paraplegic patients. Regarding tetraplegic patients, FDA has approved three devices: Ekso® (allowed only for C7 to T3 Asia Impairment Score (AIS) D patients), Indego® (C7 or below) and Hal® (C4 to L5 AIS C or D). These 3 exoskeletons can be used after SCI if UL strength is enough to allow use of assistive devices, such as crutches or walkers [255]. Other self-balancing WPE, like Atalante® or Rex®, allow ambulation without UL help or use of assistive devices [256].

Previous studies mainly focused on the use of WPE for gait rehabilitation in paraplegia. Compared to tetraplegia, paraplegic patients present greater autonomy during transfers, fit quicker into robotic devices and control independently assistive devices during autonomous walking. To this day, safety and feasibility of WPE during gait rehabilitation is only validated after paraplegia [250]. Two recent meta-analyses on walking assisted by powered exoskeletons after paraplegia demonstrated safety and indicated an improvement in walking capacities [250, 257]. In addition, some studies suggested that gait training using WPE constitutes a way to perform physical activity after SCI [250, 258, 259]. Gait training after tetraplegia is more challenging due to greater motor impairments concerning both the trunk and ULs, increased energy expenditure and cardiovascular autonomic dysfunction [249, 256, 260]. At the best of our knowledge, no systematic review has been conducted to assess feasibility, safety and potential health benefits of gait rehabilitation using WPE in tetraplegic patients.

The primary objective of this systematic review is to study whether gait training using WPE is feasible and safe after tetraplegia due to SCI. We have addressed the following question in PICO form: “Is gait training using WPE feasible and safe for adult patients with tetraplegia after traumatic or vascular SCI”? A secondary objective is to assess if walking ability improved after gait training using WPE and whether this treatment leads to additional health benefits regarding gastro-intestinal, urological, or musculoskeletal systems.

5.3 Method

Design

This review was performed according to PRISMA-S guidelines [261] and was registered in PROSPERO (CRD42020216070).

Identification and study selection

Two independent reviewers systematically searched three electronic databases (SCOPUS, PUBMED and EMBASE). The final search (Table 1) was conducted on the 1st of February 2022. All references were stored in EndNote© and FileMaker© pro version 16. After removal of duplicates, a first selection was performed through titles and abstracts screening. Studies eligibility was assessed according to the following criteria: study design of randomized and non-randomized controlled trials, prospective or retrospective cohorts, case series and case studies; participants were adults with tetraplegia, at all stages, after traumatic or vascular SCI; the intervention consisted of gait training using WPE; reported outcomes concerned occurrence of adverse events and/or relevant outcomes concerning gait at function or activity level and potential health benefits regarding gastro-intestinal, urological, or musculoskeletal systems, according to the ICF-WHO model; articles written in French or English were included. All other gait rehabilitation programs or devices, including RAGT such as the Lokomat®, were excluded. Also, studies combining gait training with any other orthosis, electrical stimulation or invasive treatment were excluded.

Table 1. Search strategy for PubMed database

Database	Search strategy
PubMed	(Rex OR ReWalk OR HAL OR Ekso* OR Indego OR WPAL OR mindWalker OR Elegs OR Exo-H2 OR Exoskelet* OR Robotic gait OR Robotic rehabilitation OR Lower extremit* robotic* OR wearable robot*) AND (Spinal cord injur* OR spinal injur* OR spine injur* OR spine injur* OR Paraplegi* OR Tetraplegi* OR Quadriplegi* OR SCI)

Then, a selection based on full text was conducted by the same two reviewers. Disagreements were resolved through discussion.

Quality and risk of bias assessments

The Downs and Black checklist (D&B) was used to assess risk of bias in included cohort or randomized control studies.

Data extraction

Data extraction was performed using the following sequence. First, we verified the type of study and whether it included a mixed population (paraplegic patients and tetraplegic patients) or a specific population (only tetraplegic patients). Then, we identified in each study the number of tetraplegic patients. Tetraplegic patients were classified according to the severity of the lesion (motor complete: AIS A or B, motor incomplete: AIS C or D) and the NLI (high=at or above C6; low=below C6). Finally, we specified the following characteristics for rehabilitation program used by each study: type of WPE used, intensity and duration of training, overground vs treadmill training, task specificity, BWSS or other walking assistive devices used.

Outcome measurements

As primary outcome, we collected all reported adverse effects and, in case of studies including both paraplegic and tetraplegic patients, we specified whether they affected a paraplegic patient or a tetraplegic patient. If the adverse events could not be precisely attributed to a specific patient, authors were contacted by mail to request access to additional information. adverse events were classified according to the following categories: musculoskeletal, cutaneous, cardio-vascular, pain, falls, fractures. adverse events were characterized as minor or serious. We defined serious adverse events as events requiring a definitive interruption of the gait training program using WPE. Finally, WPE software defects or manipulation errors were treated separately.

As secondary outcomes, we collected all the information concerning the potential additional health benefits of gait rehabilitation using WPE. We focused on various parameters in accordance with the ICF-WHO model: body function and structure (walking parameters, spasticity, pain, cardio-vascular, bladder dysfunction, neurogenic bowel and osteopenia), activities (walking tests, balance) and participation (quality of life). Regarding secondary outcomes, we only extracted data reported as a difference, subtracting pre-test score from the post-test score.

Data and statistical analysis

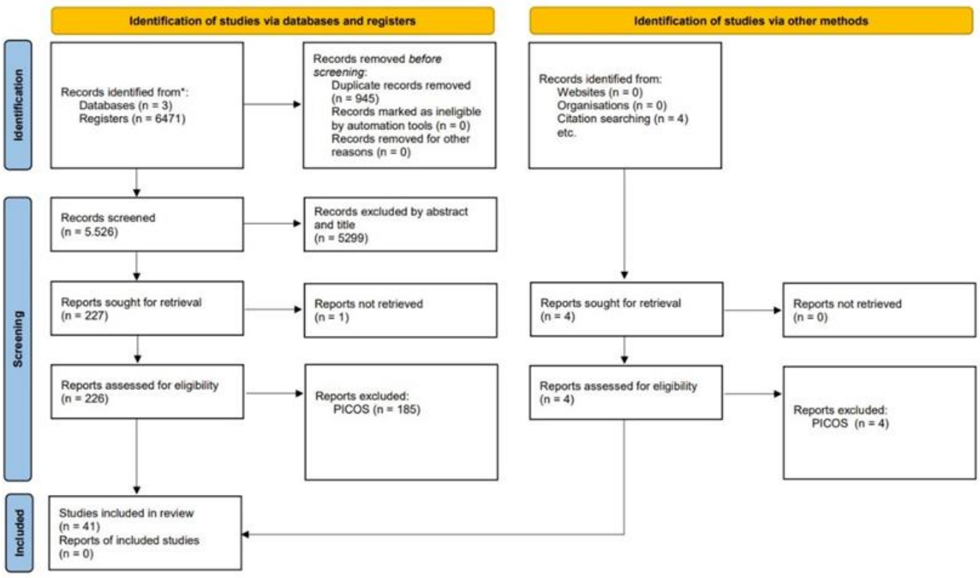
All collected data was structured in tables for qualitative synthesis and analysis. When applicable, subgroups were expressed in terms of percentage of total. Also, when possible, percentages in paraplegic patient and tetraplegic patient populations were compared using a Fischer's exact test. Statistical level of significance was set at 0.05 for all analyses.

5.4 Results

Study selection

Database search retrieved 6471 references. After removal of duplicates and initial title and abstract screening, 226 articles were selected for full text analysis. Finally, 41 studies were included in this review. Details of the selection process are illustrated in the study PRISMA Flowchart (Figure 1).

Figure 1. Flow diagram (PRISMA) of the selection process.



Study characteristics

In this review, we retained 6 randomized trials, 23 cohorts and 12 cases series. Except for 6 case series and 2 randomized trials, all studies concerned mixed populations including both paraplegic patients and tetraplegic patients.

Patient characteristics

A total of 570 patients with SCI were included in this review among which 166 (29%) tetraplegic patients. Among 166 tetraplegic patients, 26 (16%) presented with complete tetraplegia (AIS A), 71 (43%) were classified as high NLI and 17 (10%) were in the acute or subacute phase post-SCI (less than 6 months since SCI) [249, 254, 262-264]. Table 2 displays detailed information for each included study regarding severity of lesion, NLI and time post-SCI.

Gait training using WPE

Eight types of WPE used for gait training after SCI injury were identified (Table 2). Ekso® (all models combined) was the most frequently used WPE (over 56% of the studies) for gait training after SCI and the most studied in the tetraplegic patient population (78 among 166 tetraplegic patients in total). HAL® is the second most used WPE and was used in 24% of the studies including 72 tetraplegic patients. Other WPE including ReWalk®, H-Mex®, Rex®, Indego®, Angelegs® and exo-H2® were used in 1 to 2 studies for a total of 16 tetraplegic patients. Rehabilitation protocols present considerable heterogeneity among included studies (Table 2). Differences can be represented by the total number of sessions, ranging from 1 to 100. In most programs, session duration was set between 60 and 90 minutes at a frequency of 2 to 3 sessions per week.

In 73% of studies, the training protocol included overground gait training without BWSS. In all studies using HAL®, a BWSS or treadmill training were used in 100% and in 80% of studies, respectively (Table 2). Only 1 study combined a BWSS with Ekso® (4). Close supervision by one therapist is the common rule. In 3 cases, up to 3 therapists were required for assistance during transfers to fit into the exoskeleton and supervision during gait training.

Primary outcomes

This review retrieved a total of 174 adverse events (Table 3). Occurrence of adverse events (both minor and major) is significantly higher (p = 0.001) in a paraplegic patient population (n=157, 90%) compared to tetraplegic patients (n=17, 10%). Only one serious adverse event concerned a tetraplegic patient (stress fracture of tibia) [265, 266]. The 16 minor adverse events assigned to tetraplegic patients are characterized as follows: 8 cardio-vascular [267-269], 5 pressure sores [249, 270-272] and 3 musculoskeletal [273]. In addition, 32 cases of mechanical and/or software issue or a manipulation error were reported, without any consequences for the participant.

Finally, 34 dropouts were reported in total concerning both paraplegic patients and tetraplegic patients: 12 for an incomplete assessment [253, 274-276], 4 with no reason communicated [252, 254, 276], 2 linked to major anxiety diagnosed before the intervention [254], 7 due to patient withdrawal for personal reasons [252, 253, 272, 275, 277, 278], 5 caused by time restrains [267, 277-279], 1 surgery not related to the intervention [267], 3 concomitant medical issues/unrelated injuries [267, 272].

Table 2. Characteristics of included studies and tetraplegic participants grouped by type of exoskeleton used in each series.

Type of WPE	Author, year	Study design	Participants (total) (*n*)	Participants (tetraplegic) (*n*)	Mean age (tetraplegic) year ± SD	NLI		AIS score		Stage		D&B
						High	Low	A-B	C-D	Acute	Chronic	
Ekso©												
	Baunsgaard 2018 Bach Baunsgaard 2018	Cohort	52	14			3	3	11			Fair
	Chang 2018	RT	4	2	47 ± 24	1	1		2		2	Fair
	Chang 2020	Case-report	1	1	66		1	1			1	NA
	Chisholm 2017	Case-series	3	1	42		1	1			1	NA
	Delgado 2020	Cohort	12	6		6			6	6		Fair
	Edwards 2022	RT	12	6	46 ± 7.2	5	1		6		6	Good
	Escalona 2018	Cohort	13	1	42	1		1			1	Fair
	Escalona 2020	Case-series	3	1	51	1			1		1	NA
	Evans 2021 Schackleton 2021	RT	8	8	40 ± 11.2	7	1		8		8	Fair Fair
	Gagnon 2018	Cohort	14	1	42	1		1		1		Good
	Gorgey 2017	Case-series	4	2	37 ± 23.3	2		1	1		2	Good
	Hong 2020* Gorman 2021*	RT	50	14				4	10		14	Fair Fair
	Kozlowski 2015	Cohort	7	2		1	1	1	1		2	Poor
	Kressler 2018	Case-series	4	1	24	1			1		1	NA
	Lester 2018	Case-series	1	1	21	1		1			1	NA
	McIntosh 2020	Cohort	11	2	27 ± 15.6	2		1	1	2		Fair
	Ramanujam 2017*	Cohort	5	2	53 ± 1.4	2			2		2	Poor
	Ramanujam 2019*	Cohort	14	5	49 ± 9.7	3	2		5		5	Poor
	Stampacchia 2016	Cohort	21	4	53 ± 14.3		4	1	3		4	Poor
	Tsai 2020	Cohort	10	4					4	4		Fair
	Total		249	78		34	15	16	62	13	51	
Hal©												
	Brinkemper 2021	Cohort	15	4	43 ± 14.9	4			4	2	2	Fair
	Fisahn 2016	Case-series	1	1	29	1			1	1		NA
	Grasmücke 2017	Cohort	55	13		10	3		13		13	Fair
	Ikumi 2017	Case-series	1	1	19	1		1			1	NA
	Jansen 2018	Cohort	21	3	28 ± 11	2	1		3		3	Fair
	Okawara 2020	Cohort	20	10							10	Fair
	Okawara 2022	Cohort	9	6	44 ± 17.5	5	4	3	3		6	Fair
	Shimizu 2017	Case-series	4	1	20	1		1			1	NA
	Soma 2021	Case-series	1	1	47		1		1		1	NA
	Zieriacks 2021	Cohort	121	32							32	Fair

Table 2. Characteristics of included studies and tetraplegic participants grouped by type of exoskeleton used in each series (continued).

	Total		248	72		24	9	5	25	3	69	
Rewalk®												
	Benson 2016	Cohort	10	2	26 ± 4.2		2	1	1		2	Fair
	Khan 2019	Cohort	12	3		2	1		3		3	Good
	Total		22	5		2	3	1	4		5	
H-Mex©												
	Kim 2021 Park 2021	Cohort	11	1	58	1			1		1	Fair Fair
Rex©												
	Birch 2017	Cohort	20	5		5			5		5	Fair
Indego©												
	Hartigan 2015	Cohort	16	3		3		3			3	Poor
Angelegs®												
	Jang 2019	Case-series	1	1	57	1			1		1	NA
Exo-H2©												
	Pérez-Nombela 2017	Case-series	3	1		1			1	1		NA

WPE wearable powered exoskeleton, *Type of series* according to equator network website; *High* C2–C6;, *Low* C7–T1, *NLI* Neurological level of injury, *AIS* ASIA impairment scale; *Acute* < 6 months; *Chronic* ≥ 6 months; *D&B* Downs and Blacks checklist, *RT* randomized trial, *NA* not applicable

[*]Studies using Rewalk® and Ekso®

Table 3. Characteristics of gait training rehabilitation programs grouped by type of exoskeleton used in each study.

Type of WPE	Author, year	Participants (tetraplegic) (*n*)	sessions (*n*)	Frequency (sessions per week)	Time per session (minutes)	BWSS	Assistive devices	Therapists (*n*)	Treadmill
Ekso©									
	Baunsgaard 2018	14	24	3	60		✓		
	Bach Baunsgaard 2018								
	Chang 2018	2	15	5	60		✓		
	Chang 2020	1	9	2–5	60	✓	✓	2	
	Chisholm 2017*	1	10	3–4	45				
	Delgado 2020*	6	1–4	3	90		✓	1	
	Edwards 2022	6	36	3	30		✓	1	
	Escalona 2018*	1	4	2–3			✓	1	
	Escalona 2020	1	4	5	45–60		✓	1	
	Evans 2021 Shackleton 2021	8	72	3	60				
	Gagnon 2018	1	18	3	60		✓	1	
	Gorgey 2017	2	10–15	1	60		✓	1	
	Hong 2020	14	36	3	60–90		✓	1	
	Gorman 2021								
	Kozlowski 2015	2	24	1	120		✓	1	
	Kressler 2018*	1	26	1–2	60–90		✓	1	
	Lester 2018	1	3	1	<60		✓	2	
	McIntosh 2020	2	25	3	60			1	
	Ramanujam 2017	2	60–100					1	
	Ramanujam 2019	5	60–80	3–4	70–100		✓	3	
	Stampacchia 2016	4	1		60		✓	1	
	Tsai 2020	4	2–7	3	60–90		✓	1	
Hal©									
	Brinkemper 2021	4	60	5	30	✓		1	✓
	Fisahn 2016	1	60	5		✓		1	✓
	Grasmücke 2017	13	60	5	90	✓		1	✓
	Ikumi 2017	1	10	2	60	✓		3	✓
	Jansen 2018	3	60	5	90	✓		1	✓
	Okawara 2020	10	20	2–5	60	✓		1	✓
	Okawara 2022	6	20	2–5	60	✓		1	✓
	Shimizu 2017*	1	10	2	60–90	✓	✓	4	
	Soma 2021	1	13	4	40	✓	✓	1–2	
	Zieriacks 2021	32	60	5	90–120	✓		1	✓
ReWalk®									
	Benson 2016	2	20				✓	1	
	Khan 2019	3	45	3–4	60		✓	1	
H-Mex©									
	Kim 2021	1	30	3	60		✓	1–2	
	Park 2021								
Rex©									
	Birch 2017	5	1		180–240			1–2	
Indego©									
	Hartigan 2015	3	5		90		✓	1	
Angelegs©									
	Jang 2019	1	30	5	20		✓	1	
Exo-H2©									
	Pérez-Nombela 2017	1	1		<60			1	

Data reported according to the FITT principle (Hafidz 2014): Frequency, Intensity, Time, Type; *WPE* = wearable powered exoskeleton; # total number; *BWSS:* Bodyweight support system; @ condition respected or device used; * reported data concern tetraplegic participants on a mixed population

Table 4. Minor and serious reported adverse events regarding tetraplegic patients and mixed populations.

Author, year	Participants (*n*)	Minor adverse events								Serious adverse events	
		Cutaneous			Cardiovascular		Musculo-skeletal	Pain	Fall	Cutaneous	Musculoskeletal or factures
		G1	G2	OH	BPC	HT					
Tetraplegic patients											
Bach Baunsgaard 2018*	14			1							
Benson 2016*	2										
Chang 2020	1										
Chang 2018	2						1				
Delgado 2020	6	1									
Evans 2021 Schakleton 2021	8										1
Fisahn 2016	1										
Gagnon 2018*	1			1							
Ikumi 2017	1				6						
Jang 2019	1										
Khan 2019	3	1					1				
Lester 2018	1	1									
Shimizu 2017	1	1									
Soma 2021	1						1				
Tsai 2020	4	1									
Total	47	5		2	6		3				1
Mixed paraplegic and tetraplegic population											
Bach Baunsgaard 2018* Baunsgaard 2018	52	5	4	9				9			3
Benson 2016*	10	5	8					1		2	1
Birch 2017	20										
Brinkemper 2021	15										
Chisholm 2017	3										
Edwards 2022	12	5					7	2			2
Escalona 2020	3	–	–	–	–	–	–	–	–	–	–
Escalona 2018	13	–	–	–	–	–	–	–	–	–	–
Gagnon 2018*	14			6			1	5			1
Gorgey 2017	4										
Grasmücke 2017	55										
Hartigan 2015	16	2									
Hong 2020 Gorman 2021	50	39					8		2		
Jansen 2018	21	4									
Kim 2021 Park 2021	11	2							1		
Kozlowski 2015	7	1									
Kressler 2018	4										
McIntosh 2020	11	2		2					1		1
Okawara 2022	9										
Okawara 2020	20										
Pérez-Nombela 2017	3	–	–	–	–	–	–	–	–	–	–
Ramanujam 2019	14	–	–	–	–	–	–	–	–	–	–
Ramanujam 2017	5	–	–	–	–	–	–	–	–	–	–
Stampacchia 2016	21										
Zieriacks 2021	121										
Total	514	65	12	17			16	17	4	2	8

G1 grade 1, *G2*: grade 2 (Schanck 2015), *OH* orthostatic hypotension, *BPC* blood pressure changes, *HT* hypertension

*Studies where specific adverse events for tetraplegic patients are specified, but serious adverse events occurred on a mixed population

– Data not available

Secondary outcomes

Walking parameters and walking functional tests

In total, 20 studies reported outcomes separately for tetraplegic patients: 12 concerning walking parameters and 13 concerning walking functional tests (Table 4). Among them, 4 studies focusing on walking parameters showed statistically significant improvements regarding walking speed, walking distance, walking time, 6MWT, 10 meters walking test (10MWT) and Time Up and Go [262, 265, 280, 281]. In one randomized trial, including eight tetraplegic patients in the intervention group, a statistically significant improvement of approximately 60% was reported [268]. Interestingly, one tetraplegic patient improved his ASIA score [262] and another one become a walker without the exoskeleton after the WPE rehabilitation program [272]. Finally, one randomized trial showed similar improvements in walking functional tests between incomplete tetraplegic patients and paraplegic patients after a gait training program using two types of exoskeletons (Ekso® & ReWalk®). However, the same study reported greater improvement in paraplegic patients than in tetraplegic patients with complete lesions [281].

Additional health benefits

In total, 12 studies examined potential additional health benefits of gait training using WPE specifically for tetraplegic patients. These potential additional health benefits concerned various aspects of health: functional status, balance, cardio-vascular health, pain, spasticity, bowel and lower urinary function, bone mineral density and quality of life. In each case, different scales or measures have been used for each outcome. In total, 2 studies, including a total of 9 tetraplegic patients, have reported a statistically significant improvement in at least one additional health benefits: a case report reported improvement of spasticity measured with the modified Ashworth scale and a randomized trial showed improvements in cardiovascular efficiency measured with the Total Heart Beat Index [265, 271].

Finally, in 7 studies concerning tetraplegic patients, gait rehabilitation using WPE constituted a way to perform physical activity at light to moderate intensity [264, 279, 282-286]. One of these studies showed that tetraplegic patients have a higher cardiorespiratory demand during WPE gait training than paraplegic patients [284].

5.5 Discussion

Main findings

This systematic review shows that gait training using WPE for patients with tetraplegia is a feasible and safe intervention with no distinction in terms of NLI and severity of the lesion. These results are in line with previous findings regarding paraplegia [250, 257, 287]. Additionally, some studies, with an overall low level of evidence, including a small number of tetraplegic patients, suggest that gait training using WPE could lead to a reduction of spasticity and an improvement of cardiovascular efficiency [265, 271].

Gait training using WPE in tetraplegia compared to paraplegia

To this date, gait rehabilitation using WPE in tetraplegia is poorly studied which is probably due to greater requirements of tetraplegic patients during rehabilitation. tetraplegic patients often present with trunk and UL impairments which lead to higher needs in terms of time and therapist supervision, thus higher treatment costs. Indeed, tetraplegic patients require more assistance during transfers or for fitting into the WPE [256, 288, 289]. Also, a more meticulous patient selection and a closer medical supervision were deemed necessary since the risk of medical concerns, such as cardiovascular autonomic dysfunction (autonomic dysreflexia or orthostatic hypotension), is theoretically higher than for paraplegic patients [264, 290, 291]. Additionally, reduction in bone mineral density) seems to occur rapidly after SCI, leading to an increase in risk of fragility fractures [292, 293]. According to some authors, up to 46% of people with SCI will develop a fragility fracture in the sub-lesional areas within 5 years of initial injury [294, 295]. However, it has been suggested that the level of lesion does not seem to determine the severity of bone loss [296]. Concerns over these issues probably discouraged the use of WPE in patients with tetraplegia, especially when SCI is considered as “high” [255].

In some cases, special adaptations of the program intensity and content may be required. Individual adaptations can be scheduled depending on specific characteristics of each tetraplegic patients (mobility restrictions, upper and lower limb strength, autonomy during transfers, medical history [270]. tetraplegic patients need more human assistance during gait training and choice of assistive devices should be adapted depending on the NLI and the exoskeleton specificities [268]. Self-balancing exoskeletons such as Rex® or Atalante®, that don't need assistive devices or other supplemental upper body support during gait training, offer new possibilities for rehabilitation after high and/or complete tetraplegia [256].

Special considerations before starting gait training using WPE in tetraplegia

To minimize occurrence of adverse events, it seems crucial to adequately select and prepare the candidate before starting the gait rehabilitation program. First, manufacturer recommendations concerning height, weight, spasticity, range of motion and NLI, must be respected. These recommendations can vary for each device but are in their vast majority similar [255]. Second, according to some authors, before starting gait training using WPE, patients should be able to stand in a standing bar to minimize occurrence of OH during walking sessions [264, 297]. Third, cutaneous inspection of skin areas in contact with the exoskeleton (typically the lower back and thighs) [272, 278], should be performed by a rehabilitation professional, usually the physiotherapist, before and after every session [298]. The majority of adverse events identified in our review could be minimized or at least quickly solved through vigilance and specific individualized adaptations. For example, using a cushion to avoid pression sores [271] or interrupting the training program until full recovery of minor skin injuries [264].

Concerning serious adverse events, previous work focusing on gait training using exoskeletons in paraplegia calculated an estimated incidence of fractures at 3.4% [250]. In one hand, fractures can be favorized by SCI-induced osteoporosis [299] and the elevated vertical ground reaction force which have been estimated at 36% (+/- 15%) of the total bodyweight of the patient when using a WPE [268, 300]. In our review, there was only one reported stress fracture of the tibia concerning a tetraplegic patient. Distal femur and proximal tibia appear to be the most frequently concerned areas for fragility fractures after SCI. On the other hand, one randomized controlled trial suggested that gait training using WPE potentially constitutes a secondary prevention treatment of progressive decline in bone mineral density [266]. However, according to some authors, stress fracture occurrence may be underestimated [288] due to low sensitivity of conventional x-ray test and other imaging procedures, such as MRI or CT-scan, may be required for detection [267, 277]. Finally, some authors suggest that a bone mineral density test should be performed before participation in gait rehabilitation programs using WPE [277, 301]. Nevertheless, in which case a bone mineral density should be performed and how results should influence practice is still source of controversy [301, 302].

Characteristics and benefits of gait training programs using WPE in tetraplegia

In our review, most of the included studies used a training protocol similar to the one described by Asselin et al. [297]: 60 to 90 minutes per session at a frequency of 2 to 3 times per week. Total duration in weeks of gait training programs after SCI varied considerably among studies included in this review. Also, there were no specifications regarding potential need of a familiarization period with the device and whether learning curves vary among participants [297].

According to recent literature findings, WPE rehabilitation could have similar benefits in terms of improvement in walking parameters between tetraplegic patients and paraplegic patients [253, 264, 281]. Our findings are in line with recent studies concerning paraplegia regarding improvements in walking parameters such as walking speed and distance [250, 257]. Whether these improvements are more important for patients with acute and incomplete injuries, due to enhanced spinal neuroplasticity favoring motor relearning, needs to be further investigated in tetraplegic patients [257, 264, 272, 274, 281, 303-305].

In rehabilitation and research settings, gait training using exoskeletons allows tetraplegic patients to walk with a speed range from 0.11 to 0.4 m/s [276, 280, 289]. This speed may not be enough to consider the patient an outdoor walker [306] but constitutes a way to achieve indoor movements in standing position and could lead to better autonomy during activities of daily living, especially if the WPE is used in the home environment. Additionally, the use of WPE allows avoidance of prolonged sitting or decubitus. According to our findings, verticalization and movement in the WPE could lead to additional health benefits such as reduction of spasticity and improved cardiovascular efficiency [265, 271]. Outcomes concerning bone mineral density, balance, urinary tract, bowel, quality of life and pain management are poorly studied and remain controversial [251, 257, 278, 307-309]. Future studies should further investigate these potential additional health benefits.

Finally, interventions using WPE can be considered as a way to perform regular physical activity at light to moderate intensity [279] for tetraplegic patients, a population typically considered as sedentary [310]. New International Spinal Cord Society (ISCOS) recommendations suggest that, in accordance to the FITT principle of prescription (Frequency, Intensity, Time, Type) [311], patients with SCI need to perform 30 minutes of physical activity, of moderate to vigorous intensity, at a minimum frequency of 3 times per week in order to reduce risk of cardiovascular disease [250, 257, 310].

Strengths and limitations

This systematic review was conducted according to the PRISMA-S guidelines. Most selected studies were of moderate methodological quality and concerned mixed populations of both paraplegic patients and tetraplegic patients. The level of evidence of the studies included in this review is low. No publication bias assessment was performed. Also, some adverse events specific to tetraplegic patients could have been missed due to impossibility to specifically assign all reported adverse events. Quantitative synthesis was not possible due to heterogeneity of reported outcomes.

Perspectives

This review encourages inclusion of tetraplegic patients in gait training programs using WPE. Future studies should investigate efficacy of gait rehabilitation using WPE after SCI in terms of walking parameters and focus on potential additional health benefits regarding cardiovascular and musculoskeletal systems. WPE should be considered as an alternative way to perform regular physical activity after SCI. Finally, the next generation of WPE opens new perspectives in terms of assistive robotics, as support and substitution technologies in ecological or outdoor environments, leading towards new ways of autonomy-enhancing compensation after SCI.

5.6 Conclusion

Gait training using WPE is a feasible and safe intervention after tetraplegia. Patient selection should be conducted according to safety recommendations. WPE and assistive devices choice should be adapted to the patients' motor impairments. To this date, there are no specific rehabilitation protocols for tetraplegic patients and available protocols concern the entire SCI population. Some evidence suggests that gait training using WPE could lead to improvements in walking parameters, reduce spasticity and constitutes a way to perform physical activity after tetraplegia. Other potential additional health benefits concerning musculoskeletal, cardiovascular, urinary systems and quality of life should be further studied.

CHAPTER VI – General discussion & conclusions

6.1 Thesis summary

The two main objectives of this PhD thesis concerned the clinical validation of ROBiGAME's DDA mechanism and the efficacy of serious games for UL motor rehabilitation after stroke.

In a first study presented in Chapter 2, using a novel validation methodology, we clinically validated the DDA mechanism of ROBiGAME, a robot serious game developed by our team for combined cognitive-motor rehabilitation of the UL after stroke. More specifically, we evaluated whether parameters determining task-difficulty during gameplay adapted to individually match participants' degree of motor impairments and/or HSN. By studying relationships between functional evaluation scores of both motor and attentional impairments and respective task-difficulty parameters we demonstrated that task-difficulty adequately adapted to match individual degrees of impairment. This adaptation of game characteristics during gameplay, defining task difficulty, occurred rapidly within approximately a 45-minute session. Our findings demonstrate that adaptation of parameters determining motor and attentional task-difficulty can be adequately performed simultaneously, allowing combined rehabilitation with individualized levels of difficulty. Interestingly, our results suggest a task-difficulty adaptation that appears more straightforward for motor impairments, in contrast to a more challenging one for attentional impairments. Finally, our work presented in Chapter 2 recommends that automated mechanisms, used to adapt task-difficulty during training in technology-based rehabilitation, should undergo clinical validation following their development in order to verify that their functioning is optimal and that they do what they're designed for. In other words, we ought to make sure that the level of task-difficulty determined by the system during training is optimal to adequately challenge the patient in order to facilitate delivery in settings with reduced clinical supervision or during self-rehabilitation and potentially enhance efficacy of the intervention. Our work suggests that the methodology used for validation should take into direct consideration the functional status of the patient through rating scales and data-driven assessments.

The secondary objective of this PhD thesis focused on efficacy of interventions using serious games to rehabilitate the UL after stroke. The meta-analysis presented in Chapter 3 showed results in favour of interventions using serious games on UL motor function, UL activity and participation compared to conventional rehabilitation methods. Additionally, our results suggested long term retention at follow up regarding effects of serious-game training on UL function. Among key findings, our study indicated that interventions that complied with more than 8 among a consolidated set of 11 neurorehabilitation principles showed better overall effects compared to those that didn't. This finding highlighted that development of serious games in the neurorehabilitation context, no matter the device on which the serious game is implemented, should comply with at least 8 principles among a consolidated set of 11 neurorehabilitation principles described in Table 1. Our results also suggest that abiding to the neurorehabilitation principles of explicit and implicit feedback is of importance in serious-game training for UL rehabilitation after stroke.

Finally, this PhD thesis had two complementary objectives. A first concerning evaluation of efficacy of self-rehabilitation interventions for post-stroke motor rehabilitation. A second regarding feasibility and safety of WPE for gait training in tetraplegic patients after SCI.

First, the meta-analysis presented in Chapter 4 demonstrated that self-rehabilitation interventions are equally effective to conventional rehabilitation therapies for rehabilitation of motor function and activity in subacute and chronic stroke. Our analyses didn't reveal statistically significant differences when performing subgroup analysis of self-rehabilitation interventions depending on trial location, use of technology, intervention design, dose and stroke stage. These results suggest complementary use of self-rehabilitation, performed in addition to or in substitution of conventional rehabilitation therapies, in adults with subacute and chronic stroke.

Second, the systematic review presented in Chapter 5 indicates that, when an adequate patient selection is performed, WPE for over-ground gait training is a feasible and safe intervention for tetraplegic patients after SCI. Additionally, it appears that gait training using WPE may lead to improvements in gait parameters and constitute a way to perform physical activity in specific patients.

Table 1. List of neurorehabilitation principles with description established by Maier et al. [61]

Neurorehabilitation principle	Description
Massed practice	Tasks aiming to increase the number of repetitions performed
Dosage	Intensive training: more than a daily session of 60 minutes on every weekday
Structured practice	Training that includes periods of rest
Task-specific practice	Functional training relevant to ADL
Variable practice	Training that includes different types of tasks
Multisensory stimulation	Training that provides more than two types of sensory feedback
Increasing difficulty	Complexity of tasks changes depending on participants' ability, performance or time
Explicit feedback	Training that provides information about the patient's performance at the end of the task
Implicit feedback	Training that delivers information about the performance in real time such as visualization of movement or other kinematic properties
Avatar representation	Embodied training by representation of a human or body part
Use of the paretic limb	Promoting the use of the paretic limb

6.2 Efficacy of RAT and serious games for UL rehabilitation after stroke: principles of neurorehabilitation and other determinants

One of the principal components of current therapy approaches in neurorehabilitation relies on the dose-response relationship that is observed in motor skill acquisition and functional recovery after stroke [315]. A dose-response relationship is determined when “more time dedicated to learning a specific skill is associated with improved performance” [316]. In the context of UL rehabilitation after stroke, evidence suggests that more therapy time, including exercises with more movement repetitions, may enhance functional recovery [317].

The development and integration of robotic devices over the last three decades was expected to unlock the recovery potential of many patients by intensifying treatment through an increase in total number of movement repetitions per session. However, recent literature syntheses in form of meta-analyses, regarding efficacy of RAT for UL motor rehabilitation after stroke, have demonstrated small significantly better effects at the level of motor function and similar observed improvements regarding UL activity compared to usual care [318]. Additionally, both updated versions of meta-analyses covering this subject demonstrated that, although the number of included randomized controlled trials increased considerably compared to the initial versions of the reviews, the conclusions remained the same [36, 318]. In other terms, impact of RAT to enhance functional recovery after stroke appears to be comparable to conventional rehabilitation therapies, especially when therapist-led interventions are dose-matched. Although rehabilitation using robotic devices offers advantages in the precision, repeatability, and efficiency of movements performed during training, when compared to therapist-led physiotherapy, both modalities are complementary to enhance recovery. In recent years, we are consequently experiencing a progressive shift of paradigm regarding utilization of robotic devices for UL rehabilitation after stroke. This shift of paradigm might also concern other fields of neurorehabilitation, such as gait rehabilitation after SCI, in which the quantity of available data regarding efficacy of RAT is currently more restricted.

In order to better understand the reasons behind these results concerning efficacy of interventions using robotic devices focusing on UL motor recovery after stroke, multiple possible explanations have been put forward. Beyond potential explanations attributed to heterogeneity in design characteristics of trials included in systematic reviews on the topic, it appears that in order to deepen our understating we may need to further investigate towards three distinct directions.

First, although training intensity consists of a parameter of high importance to consider as we mentioned above, several questions on this regard are unanswered to this day. In stroke rehabilitation literature, there is no consensus on the way to report or measure the volume and intensity of delivered training [319]. In most cases, intensity is reported as the number of performed repetitions per session and volume or dosage is reported as the number of minutes per session or per day dedicated to therapy. Consequently, comparisons between interventions, even between robotic devices sharing similarities, constitutes a challenging task. This may explain why the optimal dosage of recommended daily RAT after stroke has not yet been determined and remains in most studies vaguely described.

Additionally, some authors have suggested that RAT may face similar limits as therapist-led interventions regarding their efficacy in this context and that although a minimum number of repetitions seems to be required to stimulate UL functional recovery, both types of interventions may be restricted to a ceiling effect [87]. Indeed, when approached through the lens of behavioural restitution of function after stroke, the extent of damage in neural pathways may determine the limits of recovery that any kind of rehabilitation treatment can induce through enhancement of neural plasticity.

Two complementary aspects that might also influence delivery and efficacy of robotic rehabilitation in this context are post-stroke fatigue and motor fatigability during training. According to previous studies, up to 70% of chronic stroke patients may present with post-stroke fatigue, a symptom related to poorer functional outcomes and reduced performance during execution of tasks of longer duration [320]. Motor fatigability, defined as 'the decline in an objective measure of physical performance over time', does not appear to correlate with post-stroke fatigue when evaluated using walking tests [321]. However, whether post-stroke fatigue and/or motor fatigability may influence delivery and outcomes of UL robotic rehabilitation remains unclear to this day. This is partially due to a lack of validated tools to measure post-stroke motor fatigability, especially regarding tasks performed using the UL [322]. Robotic devices, alongside other technology-based rehabilitation modalities, offer the possibility to measure motor fatigability during training. For example, decline in motor performance or increased assistance over the course of a robotic training session, are easily available data that could provide insight on whether motor fatigability influences UL robotic rehabilitation.

Although fatigue seems to present independently of the presence and severity of motor and/or cognitive impairments following stroke, it has been suggested that higher stroke severity is related to post-stroke fatigue of higher severity as well [322]. According to a recent update of stroke rehabilitation guidelines, it is recommended to routinely assess fatigue during early rehabilitation stages and at six months post-stroke [323]. An improved understanding of how post-stroke fatigue and motor fatigability influences performance during UL exercises and ADL training may influence the way we construct the individualised rehabilitation plan and deliver robotic therapy (which timing is more appropriate for the intervention? what is the optimal duration of the therapy session? how should explicit feedback be provided? how should task-difficulty be adapted during therapy? etc.).

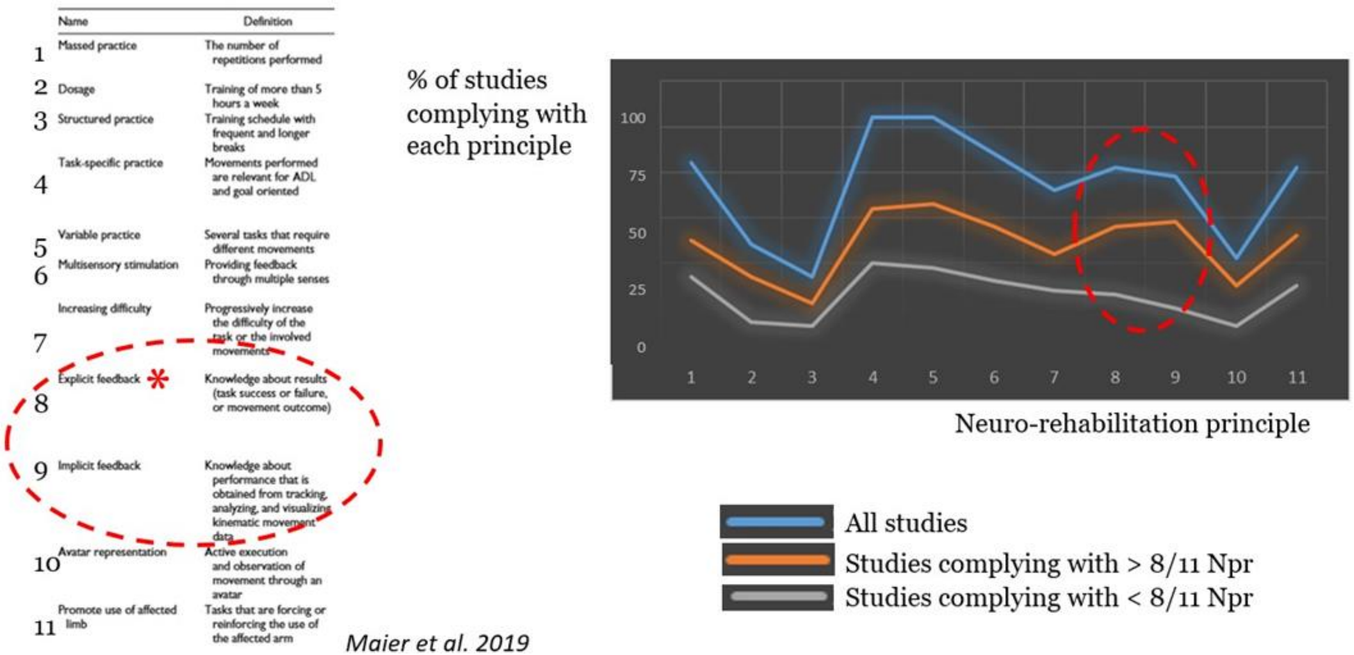
This brings us to a second point to take into consideration when it comes to include UL RAT in a rehabilitation plan after stroke. Data going back to at least fifteen years suggest that an appropriate patient selection is of high importance in order to achieve the best recovery outcome [107]. In fact, patients can be categorized in terms of recovery prognostic potential through evaluation using biomarkers [319]. It appears that some patients present with poor prognosis in terms of functional recovery of UL motor function, while others have good chances to improve when rehabilitated using appropriate interventions such as RAT [18]. Additionally, timing after stroke impacts efficacy of RAT, according to "the sooner the better" logic, especially within three months following stroke.

Finally, a third important aspect to consider concerns the structural features of the UL robotic device used during rehabilitation. In other terms, how RAT targeting the UL should be delivered? This part concerns technical characteristics of the robotic device (robotic device type, number of joints mobilised, laterality, etc.) as well as features such as the presence of a gaming component or feedback during RAT [324]. Our work offers insight concerning this third aspect.

As demonstrated in our meta-analysis presented in Chapter 3, interventions in form of serious games stimulate recovery through adherence to common neurorehabilitation principles. If we extrapolate our findings, a common rationale could potentially be applied in order to differentiate utilization and efficacy of interventions in form of RAT. Indeed, one could argue that a robotic device designed to simply perform repetitive movements in a monotonous way could not only negatively impact motivation by inducing boredom but could also present limitations in terms of learning and recovery. In other words, the evaluation of the potential efficacy of a rehabilitation intervention, such as RAT, should mainly rely on its capacity to effectively mobilize neural processes underlying recovery. In accordance with recent literature, we argue that this capacity to effectively mobilize neural processes underlying recovery seems to be determined by adherence to a consolidated set of neurorehabilitation principles presented in Table 1 [61, 62].

In addition, we suggest that depending on the context, not each single neurorehabilitation principle or cluster of principles present the same weight when it comes to their importance as an 'active ingredient' in terms of effective rehabilitation. For instance, the results of our meta-analysis, as illustrated below in Figure 1, indicate that complying with neurorehabilitation principles of implicit or explicit feedback might explain differences in efficacy among subgroup of studies complying or not with at least eight principles among the consolidated set.

Figure 1. Graph representing in detail percentage of adherence to each neurorehabilitation principle presented in Table 1 among all studies, studies with interventions complying with >8/11 and studies with interventions complying with <8/11 neurorehabilitation principles.



This finding, also in line with previous findings in scientific literature, emphasizes the importance of providing feedback information during and after training in stroke rehabilitation [61, 323]. Indeed, feedback, in form of any kind of knowledge that a participant receives during or after performing actions during RAT, can impact learning and recovery and optimize patient's motivation and engagement [25]. According to a recent Delphi study, adapting task-difficulty during training and providing verbal and/or visual feedback of results constitute two of the most important parameters that influence motivation during therapy [325]. Adding gamified components to interventions can also positively influence motivation and may improve long term adherence to treatment beyond completion of the rehabilitation program [326]. Since low motivation levels when performing exercises and low long term adherence to treatment may undermine recovery, taking motivational aspects into consideration, when choosing interventions to include in the rehabilitation plan, is of great importance.

As highlighted by a scoping review regarding factors influencing motivation during post-stroke rehabilitation, motivation may be influenced by multiple factors grouped in different categories, including intrinsic drives, extrinsic supports and intervention strategies [327]. Although this same study underlined that several gaps remain concerning the understanding of how technology-based interventions may influence motivation during rehabilitation, a recent meta-analysis suggested that VRS and serious games have the potential to improve engagement during therapy [198]. New technology-based interventions also have the potential to allow long-term tracking of changes in motivation which currently lack in studies found in literature. Finally, in case of self- or home-based rehabilitation, a recent study identified the lack of caregiver help during therapy as a potential motivational barrier [328]. In the current political and economic context, where budgetary restrictions are imposed worldwide in healthcare, being able to provide interventions that actively engage participants and preserve motivation during training becomes increasingly important. Validated tools, such as the ROBiGAME DDA mechanism, that facilitate remote or decreased therapist supervision during training can contribute to mitigate such barriers.

6.3 Task-difficulty adaptation mechanisms for UL motor and cognitive rehabilitation after stroke

In order to regulate motivation, boost engagement during training and enhance relearning, rehabilitation interventions should also adhere to the neurorehabilitation principle of increasing difficulty. According to this principle "complexity of tasks should change depending on participants' ability, performance or time" [61]. Various mechanisms to perform task-difficulty adjustment during motor rehabilitation have been previously described in scientific literature, thoroughly described in our study reported in Chapter 2. As demonstrated in this proof of concept, task-difficulty adaptation can be performed simultaneously for motor-cognitive rehabilitation during RAT. The use of a DDA mechanism, such as the one validated in our work, represents an innovative way to perform task-difficulty adaptation and creates opportunities on how to optimally challenge patients during RAT [81].

"How to determine an optimal challenge point during skill re-learning?" remains an open question in stroke rehabilitation. Based on our findings and existing literature, we suggest that algorithms developed for robotic systems aiming to provide effective DDA after stroke should include the following general principles in their configuration. Difficulty adaptation should be dictated by skills performance metrics related to stroke impairments (motor, cognitive). In other words, while performing functional tasks during training, evaluation of how successfully these tasks were performed by the patient should be based on various types of metrics. Examples of such metrics, for tasks performed on a 2-D end-effector type robot, may include the following: pulling/pushing forces, ratios of movement smoothness/straightness, reaction times, movement times, number and types of pointing errors, etc. Success rates should also be included as a performance metric in the system decision making process. It has been suggested that modulation of task difficulty based on performance constitutes an effective way to modulate practice conditions so that they maximize the potential for learning [112]. In addition, skill performance metrics should be compared to reference data collected from healthy subjects and the adult stroke population. Success rates should also be compared to a reference value, usually set at about 70 % [61]. The comparisons between the patient's performance and reference values should constitute adaptive rules by dictating how parameters determining task-difficulty fluctuate during training. Adaptive rules aim to reduce deviation between desired and actual performance, by maintaining an individualized level of challenge during training to maintain motivation and enhance relearning [112].

One of the challenges featured in our work concerns the simultaneous regulation of task-difficulty for motor and cognitive tasks. Indeed, as described in Chapter 2, although motor task-difficulty adaptation seems more straightforward, adaptation of task-difficulty regarding attentional impairments appears to be more challenging. This may be due to different reasons.

First, attentional impairments after stroke, including HSN, lead to diverse types of symptoms, such as perception-attention neglect, motor intentional aiming deficits and representational neglect, of various severities. Diverse symptom patterns and severities produce heterogeneous HSN subgroups [66]. Consequently, identification of HSN and evaluation of impairment severity is a challenging task, especially since concomitant anosognosia is frequently associated when HSN is present [329]. In most cases, in clinical practice and research, paper-and-pencil tests, such as the Cancellation Test or Line Bisection Test or Bells test, are used to identify presence of different forms of HSN [68, 88]. These visual stimulation tests, although easy to perform, consist of crossing or circling lines or objects drawn on a piece of paper and hence present limitations. Other drawing/copying and reading tests can also be used for HSN detection but present similar weaknesses to paper-and-pencil tests. Two observational assessments, the Catherine Bergego Scale or the Kessler Foundation Neglect Assessment, have also been described for HSN evaluation [69]. These assessments include additional evaluation items regarding functional difficulties and ADL limitations related to HSN. However, these observational assessments are developed uniquely for evaluation purposes, necessitate time to complete and should be performed by trained therapists. Additionally, although notable differences can be pointed out in terms of patients' profiles regarding types and severity of HSN, most of the above-mentioned assessment scales commonly constitute simple binary classifiers determining the presence or absence of impairment [9]. Currently, there is a lack of technology-based evaluation measures that can classify severity of HSN and that give access to objective quantifiable data [9].

In the study presented in Chapter 2, the MonAmour test was used to complement clinical rating scales for evaluation of HSN [65]. As detailed in our work, this evaluation test gives access to a series of data regarding attentional impairments recorded through the REAplan® robotic device. As illustrated below in Figures 3 and 4, total mean reaction times and total number of omissions asymmetry are scattered on the x-axis, suggesting that the severity of HSN is variable among participants in our study sample. Additionally, Figure 5 indicates that among participants presenting with HSN of seemingly similar severity, attentional task-difficulty level reached at the end of all sessions can differ in some cases. This may be explained by the fact that, in presence of HSN, currently available tests, such as the MonAmour test, are not able to appropriately differentiate varying degrees of impairment severity. Indeed, interpretation should be cautious because the ability of the MonAmour test to differentiate degrees of severity of HSN has not yet been validated.

Figure 3. Participants' level of attentional task-difficulty at the end of all sessions against MonAmour test scores (total mean reaction time).

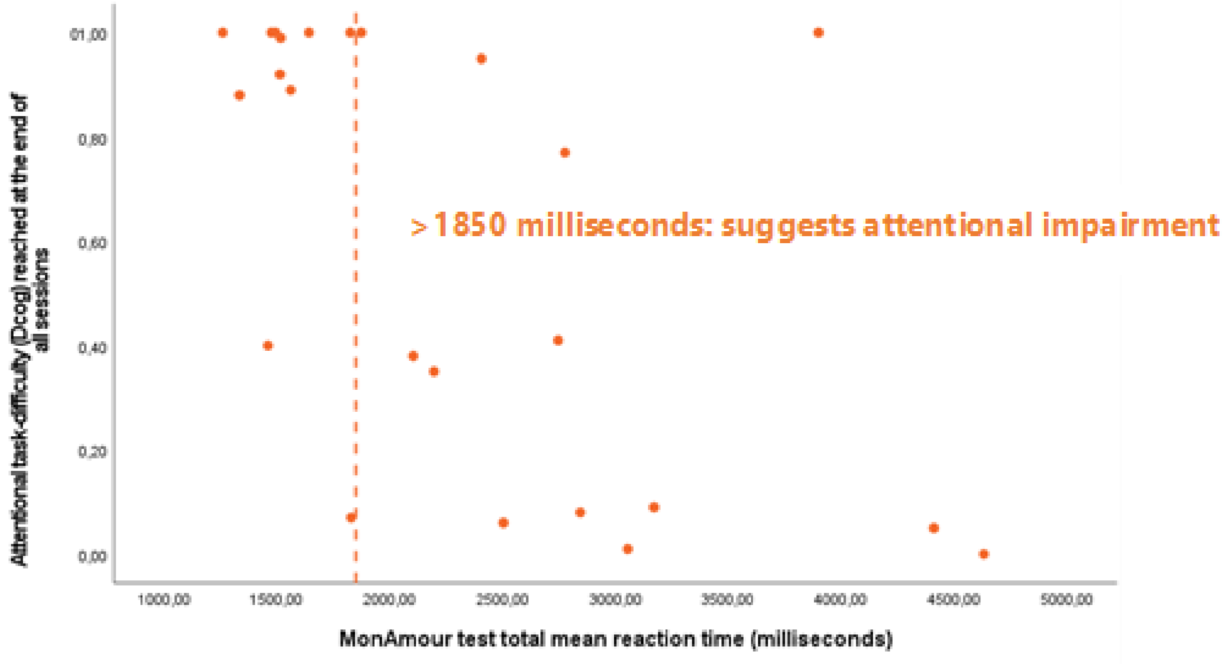


Figure 4. Participants' level of attentional task-difficulty at the end of all sessions against MonAmour test scores (total omissions asymmetry).

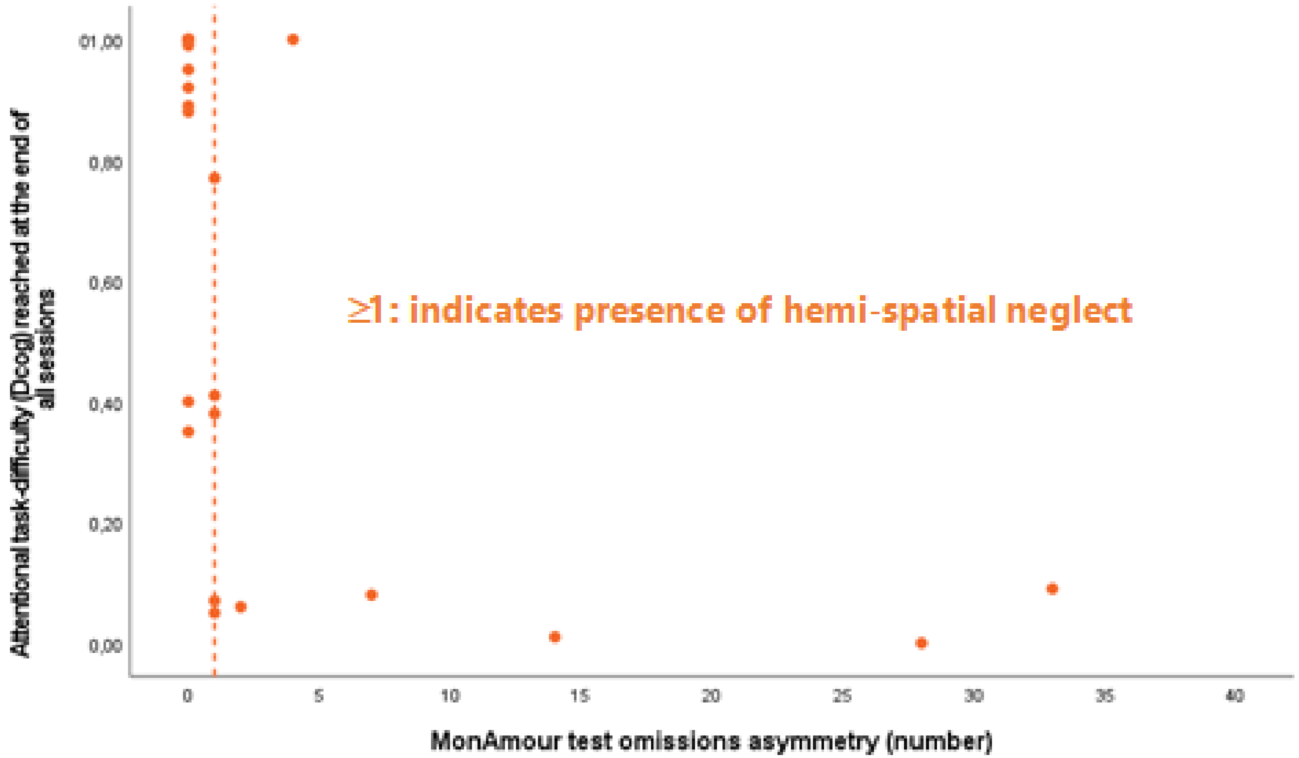
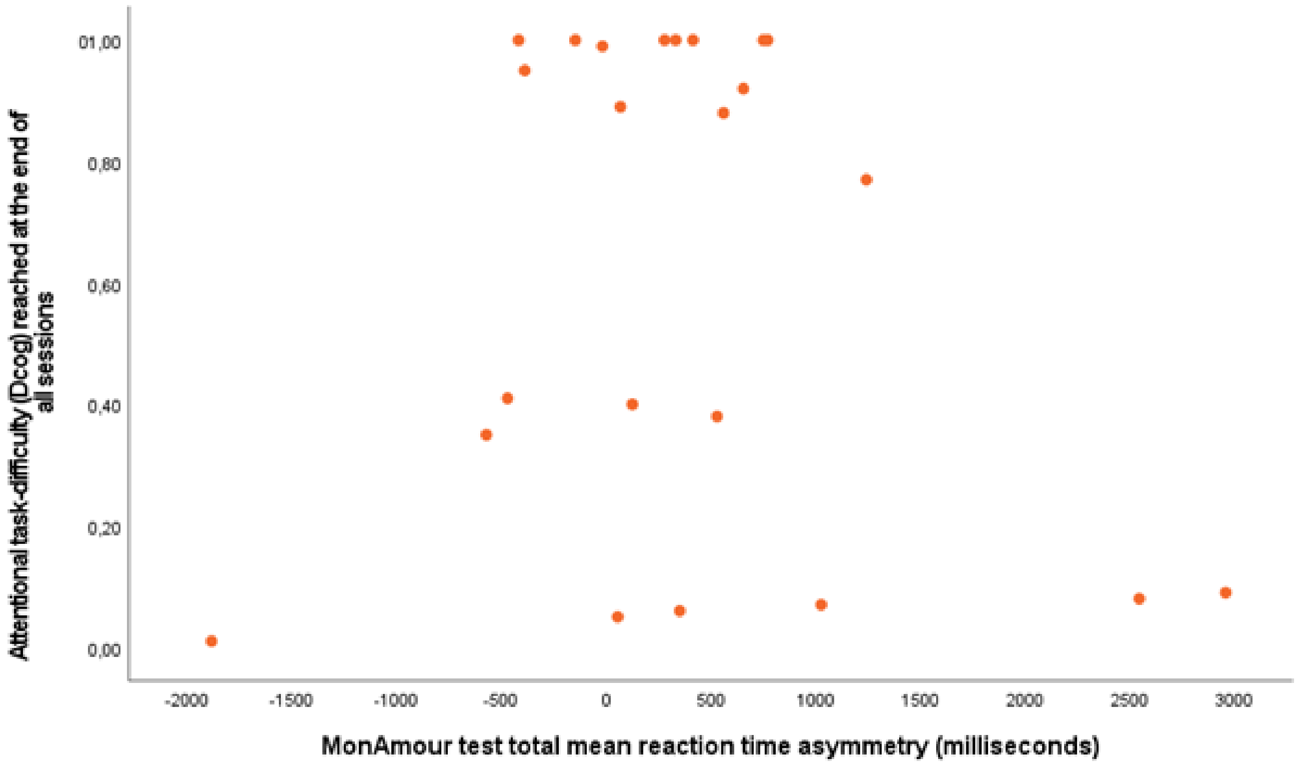


Figure 5. Participants' level of attentional task-difficulty at the end of all sessions against MonAmour test scores (total mean reaction time asymmetry).



Second, another explanation of the apparently more challenging adaptation of task-difficulty during RAT concerning the attentional aspects may be related to the fact that training is performed with the paretic limb. Obviously, the main interest of using a robotic device to challenge the patient during training is to do so using the paretic limb. However, using the paretic limb during combined motor-cognitive training directly impacts cognitive performance during exercises for some patients, particularly the ones with more severe motor impairments. Figures 6a & 6b represent evolution of attentional task-difficulty parameters over one training session of participant number 5 of our study sample. This participant presented with a severe motor impairment (FMA 14 %) but didn't present HSN. As displayed in these figures, evolution of attentional task-difficulty parameters is completely different depending on whether the game is played with the paretic limb (Figure 6a) or the non-paretic limb (Figure 6b).

Figure 6a. Evolution of attentional task-difficulty parameters over three training sessions playing with the paretic limb (Participant 5).

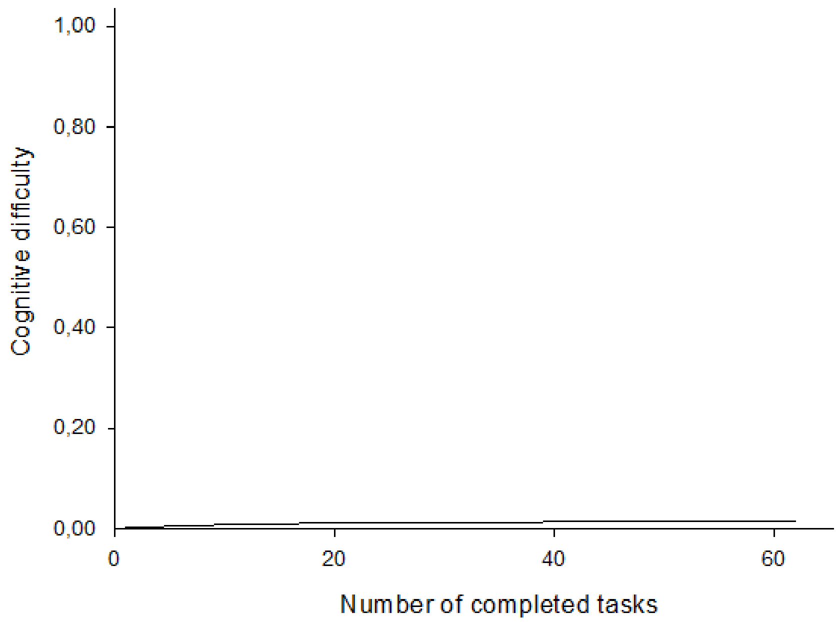
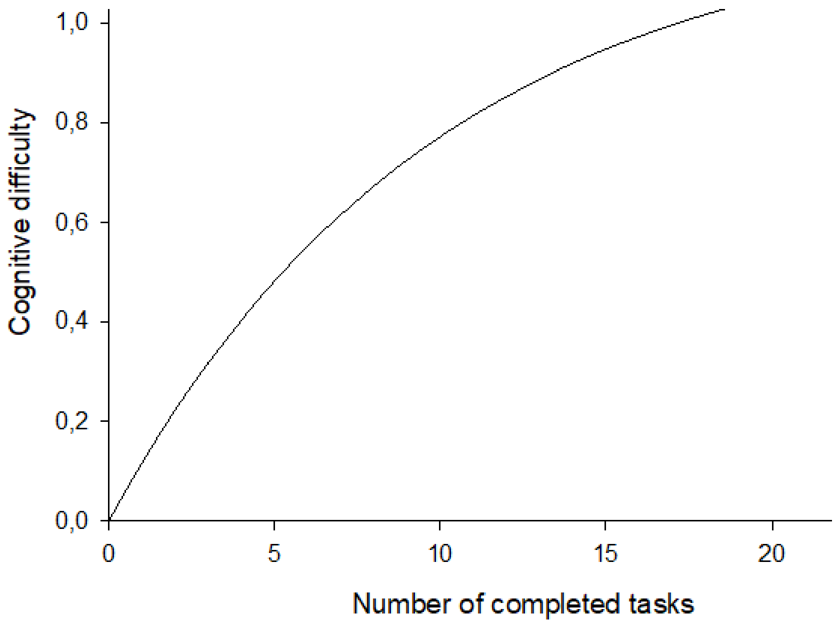


Figure 6b. Evolution of attentional task-difficulty parameters over one training session playing with the non-paretic limb (Participant 5).



Similar findings can be observed for participant number 6 of our study, presenting with a moderate motor impairment (FMA: 34 %) and HSN. As illustrated in Figure 7a, when the training is performed with the paretic limb, the patient doesn't manage to increase difficulty levels regarding attentional task-difficulty, probably due to the restriction to effectively mobilize the end-effector due to motor impairments. However, when training is performed using the non-paretic limb, the patient manages to improve the attentional task-difficulty reached during gameplay (Figure 7b).

Figure 7a. Evolution of attentional task-difficulty parameters over three training sessions playing with the paretic limb (Participant 6).

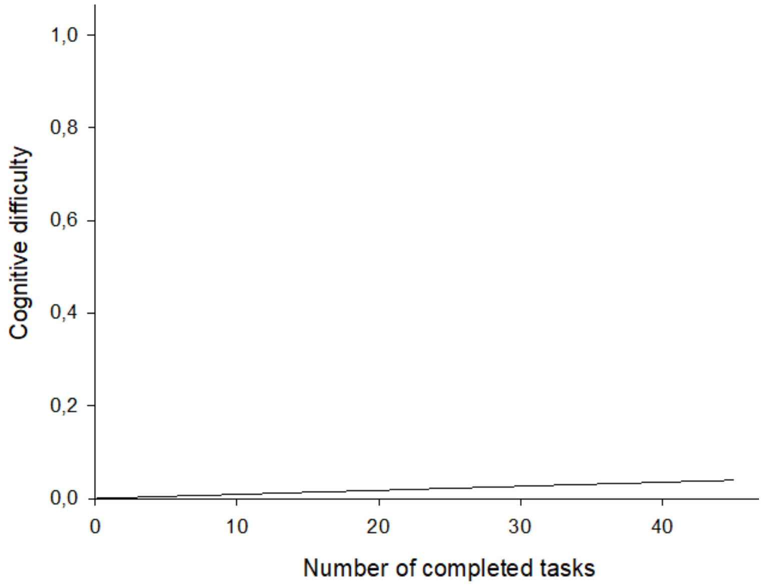
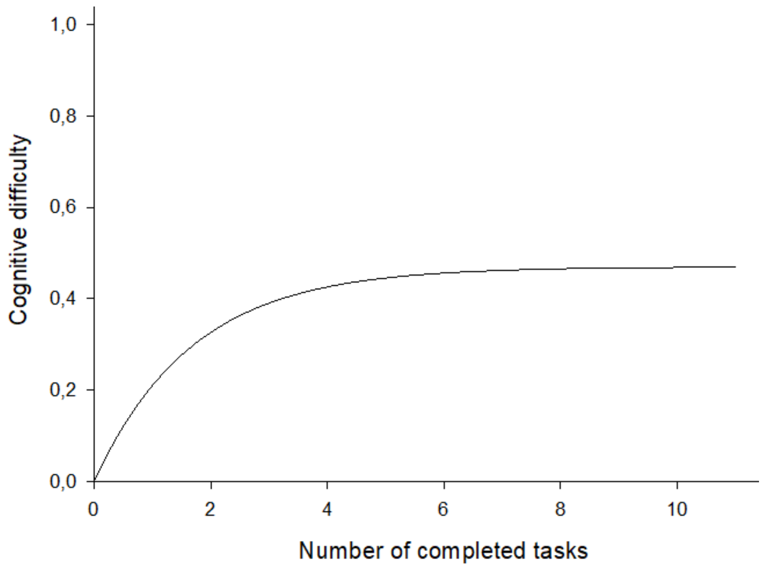


Figure 7b. Evolution of attentional task-difficulty parameters over one training session playing with the non-paretic limb (Participant 5).



These findings show that because of the heterogeneity of patient's profiles observed after stroke, different variables should be taken into consideration when determining exercise difficulty during training. Additionally, it underlines the importance of defining common rehabilitation goals in accordance with the patient's expectations. For instance, depending on the objectives set with the patient, it might be of interest to split therapy time in order to perform one part of RAT using the paretic limb and another part with the non-paretic limb. In the case of ROBiGAME, the DDA mechanism validated in our study offers the possibility to regulate task-difficulty of each subset of motor or attentional parameters independently, which constitutes a possible alternative solution.

Beyond potentially enhanced efficacy of combined motor-cognitive rehabilitation, this type of technology-based approach may also deepen our understanding on the reasons why some patient profiles have poor recovery prognosis and other respond better to certain types of therapies. Quantifiable kinematic data accessible through robotic devices complement clinical rating scales and may be used on a more regular basis to provide feedback and guide choice of rehabilitation treatments. In addition, better patient profile understanding could also ameliorate patient selection before treatment [318].

Finally, task-difficulty adaptation mechanisms, such as the ROBiGAME DDA mechanism, can contribute in the field of self-rehabilitation. Indeed, as demonstrated in our meta-analysis presented in Chapter 4, self-rehabilitation constitutes a complementary treatment that can be performed in substitution of or in addition to conventional rehabilitation therapies in order to increase total training dose or volume. Although, our results do not suggest differences in outcomes depending on whether the self-rehabilitation treatment used technology or not, this might be attributed to study design or to the characteristics of the technology used. Indeed, a recent study put forward that a sensor-based home rehabilitation program led to better outcomes compared to a paper-based program [330].

This same study suggested that in order to optimize home-based rehabilitation programs through inclusion of technology, the technology used should abide to a series of recommended design features [330]. Another study indicated that home-based rehabilitation using a wearable device improved adherence to non-supervised therapy when compared to a sham device group [331].

Since the publication of our meta-analysis, presented in Chapter 4, additional randomized controlled trials evaluating efficacy of self-rehabilitation after stroke have been published [332 - 335]. In all these recently published randomized controlled trials, the results were in line with our findings, either favouring the experimental self-rehabilitation group or demonstrating similar efficacy with the control group. In recent years, economic pressures have led to the restriction of healthcare funding and diminished availability of medical staff in hospitals [336]. In this context, interventions through self-rehabilitation have the potential to address inefficiencies in settings with limited human resources or in rural areas with limited access to rehabilitation facilities by providing self-directed training at home or at distance. Indeed, most technology-based systems described in literature can be used with no or distant therapist supervision, after an initial period of familiarisation. Moreover, rehabilitation is a dynamic process necessitating individualized repeated assessments. Validated tools, such as the ROBiGAME DDA mechanism, have the potential to optimize therapists' time, to enable patients to become more autonomous during self-assessment and to potentially improve self-rehabilitation outcomes by enhancing engagement during training and long-term adherence.

6.4 Implications of our findings for clinical practice in neurorehabilitation

The findings of this PhD thesis could influence clinical practices in neurorehabilitation in several ways.

First, the clinical validation of ROBiGAME's DDA mechanism suggests implementation in clinical practice. From now on, RAT can be delivered in a gamified way, by playing ROBiGAME sessions, to rehabilitate motor and attentional impairments simultaneously. User friendly interface and intuitive gameplay allow use with patients after stroke presenting with a wide variety of motor and/or cognitive impairments. Additionally, in case functional evaluation scores of motor or attentional impairments are available, task-difficulty indicators could be set at the appropriate level at the beginning of the training session.

Currently, RAT constitutes a therapeutic modality that should be included in every rehabilitation plan targeting UL recovery after stroke [21]. RAT should be used as an adjunct to complement conventional rehabilitation therapies and could be used as an alternative for patients with good prognosis in early phases of stroke rehabilitation. Our findings encourage delivery of RAT in form of serious games in this context. In general terms, interventions using serious games, implemented on different types of devices, constitute a treatment option to stimulate UL motor recovery after stroke, especially when adherence to at least 8 among the consolidated set of 11 neurorehabilitation principles is respected [61]. Additionally, serious games should provide feedback during training, in form of information regarding the patients' performance in real time and at the end of the performed tasks. After an initial familiarization period, RAT or serious game training could also be included in the rehabilitation plan as a form of self-rehabilitation in addition to or in substitution to other forms of therapies targeting UL motor recovery.

Beyond RAT or serious game training, self-rehabilitation should also be included in stroke rehabilitation plans as a method to increase intensity or duration of motor rehabilitation. Indeed, our results suggest that self-rehabilitation methods targeting improvements in motor function and activity are equally effective to usual care. Optimal timing and patient selection need to be further investigated [324]. In this context, self-rehabilitation should be considered as a complementary modality to in person practice. Also, self-rehabilitation will allow patients to train with reduced or distant supervision which will liberate therapists' time and create opportunities in case access to rehabilitation services is reduced.

Finally, as detailed in our systematic review presented in Chapter 5, WPE constitute a feasible and safe treatment modality for gait training in tetraplegia after SCI. Based on our results, in order to minimize occurrence of adverse events, an appropriate screening and patient preparation is required before starting a gait rehabilitation program using a WPE. In most cases, potential adverse events are easily manageable after timely identification, suggesting that therapists should remain vigilant throughout rehabilitation.

6.5 Perspectives & Future Research

Following the studies presented in this PhD thesis, multiple questions were raised. We believe that several paths related to our work, categorized in three main themes and two complementary ones, need to be further explored.

First, there is a need for future research in the field of technology-based assessment for the evaluation and follow up of motor and especially cognitive impairments after stroke. Regarding motor impairments, although a multitude of kinematic measures have been described in literature, there is a lack of consensus on which among these measures should be used in clinical practice and how they may influence choice of rehabilitation [26, 140, 337]. Recent standardization efforts underlined that kinematic measurement protocols are required in order to better understand determinants of efficacy of currently used rehabilitation therapies and deepen our understanding on recovery profiles after stroke [338]. Whether task-difficulty indicators, such as those easily accessible on ROBiGAME, may contribute to rapidly identify profiles with favourable prognosis or good responders to RAT needs to be studied. Predictive models based on similar robotic parameters have been previously described in literature regarding recovery of walking ability [339]. Concerning cognition, as highlighted in a recent systematic review, there is a lack of evaluation tests for identification of subtypes of HSN and stratification in terms of severity when this impairment is present [9]. As mentioned above, most available tests allow us to identify the presence or confirm the absence of HSN, without contributing with additional information. We believe that this may constitute an explanation of why adaptation of task-difficulty appears to be more challenging regarding cognitive compared to motor aspects, as detailed in the proof of concept in Chapter 2. Consequently, development of evaluation tests for HSN on robotic devices or VRS, giving access to objective quantifiable data on impairment severity, will contribute to better determine patients' profiles and help with future task-difficulty validation procedures. Development efforts towards that direction, with immersive or non-immersive systems, using haptic sensors or eye tracking technology, are already ongoing in healthy and post-stroke populations [340, 341].

A second area of investigation envelops the identification of certain subpopulations of patients that might benefit most from specific interventions. Recent data suggest that patients with moderate motor impairments, in the acute and subacute phases after stroke, might benefit more from intensive RAT compared to those with severe impairments [18]. Similarly, serious game training might be more beneficial to certain subgroups of patients sharing common characteristics, such as for example presenting motor and attentional impairments simultaneously or presenting lack of motivation and engagement during therapy. Additionally, some authors have argued that populations included in meta-analyses evaluating efficacy of RAT for UL rehabilitation after stroke are too heterogeneous which might mistakenly lead to inaccurate conclusions regarding efficacy of RAT in specific subgroups of patients [318]. In other words, commonly used study designs and inclusion criteria might be inappropriate to identify good responders to treatment. Consequently, instead of studying efficacy of ROBiGAME compared to usual care, which would be the next logical step following our work, it might be of interest to research potential differences in efficacy when treatment is applied to different subgroups of patients.

In complement to the above information, it has been demonstrated that patients with favourable biomarkers in early phases post-stroke present good prognosis in terms of UL motor recovery [319]. Currently, prediction models using artificial intelligence are developed based on motor evaluation data and consequently solely concern prognosis of motor recovery [342]. Future models should further include parameters for prediction of functional recovery in ADL, combining both motor and cognitive impairments.

A third important topic that should be analysed in future studies concerns the adherence of patients to rehabilitation and their motivation during training sessions. Both two parameters constitute key aspects of successful rehabilitation. As showcased in our meta-analysis presented in Chapter 3, efficacy of interventions using serious games seems to be influenced by fulfilment of more than 8 neurorehabilitation principles among a consolidated set of 11 [61]. However, how gamification of interventions might impact efficacy indirectly by improving motivation during training and adherence to treatment on the long term remains poorly studied. As mentioned above, a recent Delphi study pointed out that interventions with a gaming component, with individualized levels of task-difficulty, positively influence motivation and performance during therapy [325]. Future studies should focus on how serious game training can be efficiently used to modulate motivation, performance during training and long term adherence to treatment. Additionally, standardisation efforts should be pursued in this direction, notably concerning the methods or metrics used to evaluate motivation, volume or dosage of therapy and motor fatigability and performance during training.

Finally, findings of studies presented in Chapters 4 & 5 push boundaries for additional research in respective fields. The validation of ROBiGAME's DDA mechanism creates opportunities for self- and tele- evaluation and home rehabilitation. In fact, after a period of initial guided training and familiarization, evaluation and serious game training could be performed autonomously, with no or distant supervision. Also, efficacy of WPE for gait training could now be assessed in tetraplegia after SCI. Beyond gait rehabilitation, we should also study whether interventions using WPE can be considered as an alternative way to perform regular physical activity, at light to moderate intensity, for tetraplegic patients. Lastly, the next generation of WPE opens new perspectives in terms of assistive robotics, as support and substitution technologies in ecological or outdoor environments. The possibility of integrating WPE as a new way of autonomy-enhancing compensation after SCI should be further assessed.

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List of abbreviations

SCI = spinal cord injury

WHO = World Health Organization

ICF = International Classification of Functioning, Disability and Health

UL = UL

ADL = activities of daily life

RAT = Robot assisted training

BWSS = body weight support systems

WPE = wearable powered exoskeletons

VR = virtual reality

VRS = virtual reality systems

HSN = hemi-spatial neglect

DDA = dynamic difficulty adjustment

FMA-UE = Fugl-Meyer Assessment for the Upper Extremity

ARAT = Action Research Arm Test

D = Task-difficulty parameters

RCT = randomized controlled trials

BBT = Box and Block Test

WMFT = Wolf Motor Function Test

SIS = Stroke Impact Scale

SD = standard deviation

SMD = standardized mean difference

CI = confidence interval

NLI = neurological level of injury

TAGT = therapist-assisted gait training

RAGT = robot-assisted gait training