Universidade de Aveiro Secção Autónoma de Ciências da Saúde
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Vítor Pedro Tedim Ramos Cruz

New tools for cognitive and motor rehabilitation: development and clinical validation

Novos métodos de reabilitação cognitiva e motora: desenvolvimento e validação clínica

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Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Doutor em Ciências e Tecnologias da Saúde, realizada sob a orientação científica do Professor Nelson Fernando Pacheco da Rocha, Professor Catedrático da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro e co-orientação da Doutora Maria Paula Mourão do Amaral Coutinho, Neurologista do Centro de Genética Preditiva e Preventiva, Instituto de Biologia Molecular e Celular da Universidade do Porto.

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Às casas, que são família.
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keywords

neurorehabilitation, brain plasticity, cognitive training, motor training, modulated relearning, stroke, dementia, e-health systems, medical devices, collaborative networks.

abstract

Nervous system disorders are associated with cognitive and motor deficits, and are responsible for the highest disability rates and global burden of disease. Their recovery paths are vulnerable and dependent on the effective combination of plastic brain tissue properties, with complex, lengthy and expensive neurorehabilitation programs.

This work explores two lines of research, envisioning sustainable solutions to improve treatment of cognitive and motor deficits. Both projects were developed in parallel and shared a new sensible approach, where low-cost technologies were integrated with common clinical operative procedures. The aim was to achieve more intensive treatments under specialized monitoring, improve clinical decision-making and increase access to healthcare.

The first project (articles I – III) concerned the development and evaluation of a web-based cognitive training platform (COGWEB), suitable for intensive use, either at home or at institutions, and across a wide spectrum of ages and diseases that impair cognitive functioning. It was tested for usability in a memory clinic setting and implemented in a collaborative network, comprising 41 centers and 60 professionals. An adherence and intensity study revealed a compliance of 82.8% at six months and an average of six hours/week of continued online cognitive training activities.

The second project (articles IV – VI) was designed to create and validate an intelligent rehabilitation device to administer proprioceptive stimuli on the hemiparetic side of stroke patients while performing ambulatory movement characterization (SWORD). Targeted vibratory stimulation was found to be well tolerated and an automatic motor characterization system retrieved results comparable to the first items of the Wolf Motor Function Test. The global system was tested in a randomized placebo controlled trial to assess its impact on a common motor rehabilitation task in a relevant clinical environment (early post-stroke). The number of correct movements on a hand-to-mouth task was increased by an average of 7.2/minute while the probability to perform an error decreased from 1:3 to 1:9.

Neurorehabilitation and neuroplasticity are shifting to more neuroscience driven approaches. Simultaneously, their final utility for patients and society is largely dependent on the development of more effective technologies that facilitate the dissemination of knowledge produced during the process. The results attained through this work represent a step forward in that direction. Their impact on the quality of rehabilitation services and public health is discussed according to clinical, technological and organizational perspectives. Such a process of thinking and oriented speculation has led to the debate of subsequent hypotheses, already being explored in novel research paths.

palavras-chave

neurorreabilitação, plasticidade cerebral, treino cognitivo, treino motor, reaprendizagem modulada, acidente vascular cerebral, demência, sistemas e-saúde, dispositivos médicos, redes colaborativas.

resumo

As doenças do sistema nervoso estão associadas a défices cognitivos e motores, sendo responsáveis pelas maiores taxas de incapacidade e impacto global. A sua recuperação é difícil e depende em simultâneo da plasticidade cerebral e de programas de neurorreabilitação complexos, longos e dispendiosos.

Este trabalho explora duas linhas de investigação, que visam soluções sustentáveis para melhoria do tratamento de défices cognitivos e motores. Ambos os projetos foram desenvolvidos em paralelo, partilhando uma abordagem assisada onde se combinam tecnologias de baixo custo com processos clínicos comuns. O objetivo era obter tratamentos mais intensivos e supervisionados, melhorar o processo de decisão clínica e eliminar barreiras no acesso aos cuidados de saúde.

O primeiro projeto (artigos I – III) permitiu o desenvolvimento e avaliação de uma plataforma online para treino cognitivo (COGWEB), adequada para uso intensivo, em casa ou instituições, e num largo espectro de idades e doenças com envolvimento das funções cognitivas. A sua usabilidade foi testada numa consulta de memória, sendo de seguida implementada numa rede colaborativa que envolveu 41 centros e 60 profissionais. A taxa de adesão aos planos de treino cognitivo online foi 82,8% aos 6 meses, verificando-se uma intensidade média de 6 horas/semana.
O segundo projeto (artigos IV – VI) originou a construção e validação de um dispositivo de reabilitação inteligente para doentes com acidente vascular cerebral (AVC). Permite estímulos proprioceptivos no lado hemiparético, enquanto caracteriza o movimento tridimensional em ambulatório (SWORD). A estimulação vibratória foi bem tolerada pelos doentes e um sistema automático de caracterização motora revelou resultados comparáveis aos de uma escala utilizada frequentemente na prática clínica. O sistema integrado foi testado num ensaio clínico randomizado e controlado com placebo para avaliação do impacto numa tarefa de reabilitação motora na fase subaguda após AVC. O número de movimentos correctos numa tarefa mão-boca aumentou em média 7,2/minuto, enquanto a probabilidade de ocorrência de erro se reduziu de 1:3 para 1:9.

A neurorreabilitação e a neuroplasticidade têm incorporado abordagens de múltiplos domínios das neurociências. Em simultâneo, a sua utilidade para os doentes e sociedade está dependente do desenvolvimento de tecnologias mais eficazes que facilitem também a disseminação do conhecimento entretanto produzido. Os resultados obtidos através do presente trabalho representam um passo adicional nessa direcção. O seu impacto na qualidade dos serviços de reabilitação e saúde pública são discutidos segundo perspectivas clínica, tecnológica e organizacional. Este processo de reflexão foi gerador de novas hipóteses, algumas já em exploração através de linhas de investigação específicas.

Contents

Abbreviations

CACAO – Computer aided cognitive assessment online

CHEDV – Centro Hospitalar de Entre o Douro e Vouga

COGWEB – Web-based cognitive training system

DR – Diário da República

e-health – healthcare practice supported by electronic processes and communication

EPIPorto – Adult cohort of the Institute of Public Health, University of Porto

FCT – Portuguese national funding agency for science, research and technology

L-DOPA – Levodopa

NASA – National Aeronautics and Space Administration

PCT – Patent cooperation treaty

PPP – Patent pending

PT – Portugal

R&D – Research and development

SMS - Short messaging service

SPAVC – Portuguese Stroke Organization

SWORD – Stroke wearable rehabilitation system

TRL – Technology readiness levels

US – United States

USDoD – United States Department of Defence

WMFT – Wolf motor function test

WO – World Intellectual Property Organization

Publications

The results presented in this thesis are part of the following list of publications and outcomes, organized by category (patents, papers and books) and descending chronological order:

Patents

Bento VF, Ribeiro DM, Cruz VT, Colunas MF. "Quantification method using a tunnel of motion". US Patent Pending, Serial No: 61/767,367 (February, 2013); PCT/PT2014/000014; WO 2014/129917 A2.

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Cruz VT, Pais J. "Sistema auto-adaptativo para reabilitação de funções superiores no domicílio sob supervisão especializada". PPP 43049/10; PPN105496.

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Part I – Introduction

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1. Motivation

As a clinical neurologist, I have long dedicated special attention to an outpatient memory clinic and all phases of stroke care. This combination of settings led to an increased exposure to the diversity of cerebrovascular diseases and dementia. Among neurological disorders, these are two of the most disabling groups of diseases due to the cognitive and motor deficits associated with them. In this context, the tremendous difficulties that health professionals, patients and their relatives have to endure, in order to guarantee only substandard rehabilitation programs in Portugal, became increasingly clear.

During clinical and basic research activities in the area of neurological sciences, I was exposed to such diverse fields as genetics, epidemiology, hereditary ataxias, hereditary spastic paraplegias, dementia and stroke. Throughout that experience, I came into contact with a wide range of health professionals dedicated to the research and treatment of neurological conditions, as well as a variety of talented engineers devoted to health technologies. Somewhere during this learning path in neurosciences I realized that it was feasible to assemble a research & development (R&D) team and to design and validate innovative technical solutions targeted at some of the major problems which are faced daily whilst rehabilitating our neurological patients.

This was the trigger to carry out this work.

2. Problem definition

Neurological disorders are commonly associated with a variety of cognitive and motor deficits that originate very high disability rates and an ever increasing demand for healthcare services[1]. Amongst all major groups of diseases, neurological disorders are the most disabling, representing the highest contribution to the global burden of disease worldwide (6.3%)[1]. The value may be as high as 10.9% for high income countries or 11.2% in the European Region. It is estimated that by 2020 this figure may reach 14.7% for all neuropsychiatric disorders. These values correspond to 15 to 30 years of life lost adjusted for disability per 1000 inhabitants each year[1].

Irrespective of their cause (e.g., stroke, brain injury or dementia), cognitive and motor impairments rarely recover spontaneously or completely[2,3]. Once established, brain damage is difficult to revert and pharmacological tools with a confirmed positive effect are scarce[4-6]. The recovery process is typically slow and vulnerable. It relies on the remaining plastic properties of the remaining brain tissue and is highly dependent on complex and intensive assisted rehabilitation programs[7,8].

Neurorehabilitation programs have proven efficacy in the compensation, amelioration and stabilization of deficits in several diseases and nosological models[9-21]. Similarly to other rehabilitation processes, effective outcomes always depend on the timely onset, intensity and specificity of the treatments[3,6,22-24]. However, despite being accepted as a fundamental component of current treatment plans, there are strong restrictions on access patients have to such therapies[1,18,25-27]. These programs commonly require multidisciplinary teams, are usually performed in hospital settings, away from the patient's home, and imply the presence of a relative (requiring enormous effort on the part of patients, families and institutions)[27]. This combination of characteristics generates a large economic burden for both the health system and families[28,29]. Additionally, it limits the efficacy of the treatment programs because it increases the difficulty to enrol in rehabilitation sessions in due time (early after injury or disease onset) and to attain the high intensity, duration and quality of treatment necessary to foster nervous system plasticity[22,30].

Given the massive burden associated with neurological diseases it is currently recognized that dedicated health services and resources available worldwide are disproportionally

scarce[1,31]. Therefore, health systems may be unprepared to address the rise in the prevalence of disability resulting from neurological or mental diseases. In this respect, health care delivery processes are recognized as poorly organized, lacking efficacy, and late to incorporate technological innovation and to readapt[31-33]. For example, in stroke rehabilitation, a recommendation of an average of three hours of rehabilitation per day, seven days per week is widely recognized by experts[34-37]. Nonetheless, in a country like Canada, known for one of the more comprehensive best practice recommendations for stroke care[38], three out of four people who have had a stroke which is severe enough to require hospital admission fail to be sent to rehabilitation[39]. In addition, the number of beds and types of services vary widely, as does the proportion of specialized human resources (physiotherapist to patient ratio can go from 1:7 to as low as 1:16), and the daily distribution of time by stroke patients[39,40]. In the United Kingdom, patients were engaged in therapy for less than 15% of the working day and spent nearly 65% of their therapeutic day sitting, lying, or sleeping[41], with similar findings in other European countries[42] and the United States[43].

In spite of the major problems related with people's access to neurorehabilitation care, scientific advances have improved our knowledge of the genetic, molecular, cellular, physiological, neural network and behavioral adaptations that support the recovery of cognitive and motor functions[44,45]. This new understanding has been giving origin to novel types of therapies, centered on the promotion and modulation of neuroplasticity, mechanisms of learning and memory, neurogenesis and axonal regeneration, either through pharmacological or nonpharmacological strategies[46-48].

Future training interventions, irrespective of their modality (e.g., cognitive, behavioral or motor), setting (e.g., home or institutionally based), mode of use (e.g., isolated or in combination with drugs) or disease being treated, will require more specific and controlled methods, patient monitoring of real-life functioning at home and thorough evidence from adequately powered clinical trials with direct measures of cognitive and physical functioning[49-52]. Finally, all aspects of neurorehabilitation are shifting to more neuroscience driven approaches and their final utility for patients is largely dependent on the development of more effective solutions (clinical and technological) that facilitate the extensive application of all knowledge being produced[46,51,53].

3. State of the art

a) Neurorehabilitation

Among medical specialities, rehabilitation has been one of the slowest to develop a basic science framework and to establish strong evidence-based practices, mainly due to a large pressure for clinical services combined with a scarcity of experienced practitioners during its beginnings[54]. At the same time and until recently, neurology was erroneously considered by some as a discipline devoted mainly to the diagnosis and characterization of diseases of the nervous system, with limited engagement with therapies that provide benefits for patients[55,56]. Nowadays we are witnessing a definite trend in the opposite direction in both domains and neurorehabilitation is emerging as a clinical subspecialty engaged in the restoration and maximization of functions that have been disturbed due to injury or disease of the nervous system[54,56]. Although neurorehabilitation was traditionally focused on motor retraining, some of the most disabling conditions are related with impairments in other domains, such as cognitive and behavioral functions, which have specific approaches within the rising field of neuropsychological rehabilitation[54]. Other important new domains of neurorehabilitation are autonomic and sensory functions, which share similar scientific principles and assume greater importance in integrated recovery programmes[54].

The maturation of this new discipline is paralleled by no less than a revolution in the science of neuroplasticity and regeneration of the human nervous system during the last 20 years[6,54,57]. This background, together with the growing commitment to evidence-based medicine, currently provides a rigorous scientific framework for neurorehabilitation and its endeavour to relieve human suffering resulting from neurological and psychiatric diseases[54,58].

b) Brain plasticity

Neuroplasticity can be defined as the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganizing itself[6]. This property is supported on several systems, network structures and cellular, membrane and molecular mechanisms, and occurs in many forms and contexts throughout life. It is important for learning and maturation of the normal nervous system, behavior adaptation and also to recover or compensate dysfunction

after injury or degenerative processes[6,54,59]. Over the years, major advances in the understanding of the mechanisms that support neuroplasticity have been brought to light by researchers in the fields of nervous system injury and stroke, mental disorders and addiction, developmental disorders, ageing and neurodegeneration[6,54].

Brain plasticity uses a limited repertoire of biological events across numerous contexts and some basic principles have been evidenced across diverse central nervous system models[6]. It may occur spontaneously or be modulated through specific exposure or training, and so is experience dependent. Time sensitivity is always present, either in learning processes or after injury. The overall cognitive status of an individual patient and in particular motivation and attention are very important for long-term results. Finally, in addition to being a crucial mechanism for recovery and learning, neuroplasticity is not always adaptive or associated with a gain in function. Sometimes it can be deleterious, may lead to an increase in injury, loss of function, be disturbed by compensatory behaviors or have a mental cost (e.g., epilepsy, chronic pain, spasticity, dystonia, addictive behaviors and dementia)[6,57,59].

To better understand the applicability of neuroplastic principles across very diverse clinical contexts of the human being, some important conditions and nosological models are used here as examples: learning, developmental disorders, stroke and brain injury, psychiatric disorders, neurodegenerative disorders and ageing.

Learning

Human beings have a tremendous ability to learn, acquire new skills and change behavior. Learning is present throughout normal life, from birth and development to ageing, and is critical for the current understanding of most diseases that affect the human brain and its response to treatment[60]. Although the underlying mechanisms of learning are far from being understood, they are supported by neural networks and have a lot in common with what it is referred to today as neuroplasticity[60]. There are, unquestionably, gradients in the ability to learn new motor, cognitive or behavior skills. These may arise from genetic differences among individuals, age, specific time-windows and practice exposure throughout life or disease[60,61].

Learning and training were traditionally viewed as tightly linked in all domains, from motor skills, to memory and behavior. Therefore, learning that emerged as a result of training was specific to the particular stimuli, context and tasks. This fact has become increasingly relevant due to its impact on neurorehabilitation and education programs. For instance, it is of little use to be very proficient in a hand-to-mouth task in therapy if it does not also improve the ability to reach a glass at a dinner table. In a similar manner, it is of little benefit for young scholars to solve math problems in a classroom if they cannot apply that knowledge to solve identical problems outside a classroom context[60].

Current knowledge has been shifting this paradigm dramatically to a more "learning to learn" concept, with several approaches proving that training conditions can in fact produce observable benefits for untrained skills and tasks either in normal or disease conditions[60,62]. Some good examples are musical abilities and training[63-65], cognitive training to improve reading and writing skills in school age children with learning disabilities[66], the use of videogames for therapeutic purposes[60], athletic training[67], working memory training[68], cognitive stimulation in the elderly[30] or even the ability to learn through imagery, without actual physical training[69]. Additionally, infant, adolescent or even adult cognitive training was shown to produce structural changes and long term benefits on the ability to learn in adulthood, in clear connection with the growing attention given to cognitive reserve[61,70-72]. Despite being a largely unexplored field, the factors that promote learning to learn are of crucial importance in order to understand the key concepts underlying generalizations in learning, the modulation of intensive training programs and the successful design of rehabilitation interventions[60,73].

Developmental disorders

Congenital and acquired pediatric disorders combine several mechanisms of injury with the singular plastic properties of a developing nervous system[6]. The final functional outcome of an insult is highly dependent on the timing, chiefly with respect to age[74-76] or to critical developmental periods[77-81]. As an example, congenital hemiplegia (unilateral cerebral palsy) can result from a variety of brain lesions, with the types of impairment, plastic phenomena, response to interventions and functional outcomes being highly dependent on the timing of insults[82]. Some special expressions of neuroplasticity are characteristic of the early stages of a developing brain. Cross-modal plasticity, defined as

the capacity to reorganize sensory maps in response to normal input deprivation from a particular modality is one such example[83]. More dramatically, transposition of functions from one side of the brain to the other can occur after severe but very early damage to a dominant left hemisphere, with the right hemisphere assuming control of language or ipsilateral body movements[84,85]. Nonetheless, it is noteworthy that early brain injury can also impair subsequent plasticity[86]. The physiological mechanisms that support developmental neuroplasticity may be related with the large quantities of neurons and synaptic connections in the early postnatal period, which undergo extensive changes through competitive experience during the maturation process. Furthermore, other processes like myelination, extracellular matrix development and maturation of inhibitory circuits may be crucial for the definition of critical periods during aging[6].

Neuroplasticity during development can also be adaptive or maladaptive[6]. The age-dependent recovery of language and motor functions after hemispherectomy for treatment of intractable epilepsy and the successful adaptation to a cochlear implant in early childhood represent two good examples of the adaptive plasticity[6]. After hemispherectomy, the transferal of motor and language functions to the remaining hemisphere is impressive, but highly dependent on age, the most remarkable changes occurring under the age of six years[74,75,87,88]. These findings are most striking if the fact that this phenomenon occurs in a very abnormal brain is taken into consideration. Cochlear implants in congenitally deaf children show the best results within the first years of life, when central auditory pathways are more plastic. After the age of 7, although beneficial, cortical reorganization is always abnormal[81,89]. Maladaptive plasticity can occur, for example, in the context of early sensory deprivation, either in the auditory or visual systems. The lack of exposure imposed by congenital deafness or blindness (e.g., cataracts) may result in a failure to connect secondary with primary cortical areas, preventing important feedback loops[81,90]. These areas may then become available to other non-deprived modalities[91].

Finally, some metabolic and genetic pediatric diseases may have a diffuse effect on neuroplasticity due to interference with specific cell types, neurotransmitters and hormones, all of which are important modulators of neuroplasticity (e.g., congenital hypothyroidism, phenylketonuria or Down syndrome)[92]. When feasible, the correction of these defects, even in adulthood, may have a significant effect on neuroplasticity[92].

Stroke and brain injury

An area where neuroplasticity has been extensively studied is motor recovery after stroke[6]. Injury to a primary motor region can originate intra-hemispherical changes in representational maps (e.g., hand or face area)[93-96] or inter-hemispheric changes with an increase in activity over the uninjured side in relation to movement[97,98]. More diffuse changes in cortical connectivity, in response to focal injury, have also been evidenced in subcortical stroke models[99,100]. A consistent functional imaging finding after stroke is the activation of contralesional primary motor cortex and bilateral premotor areas[101]. However, good functional outcomes are clearly related with recovery of normal patterns of recruitment of original functional networks rather than with contralesional activity[101,102]. After stroke, besides motor deficits, multiple brain systems and human behavior important for motor relearning are often affected[103], even in patients with no detectable motor or sensory deficits[104]. Cognitive recovery after stroke, namely with regard to language, spatial attention and neglect, has showed similar results in terms of restoration and rebalancing of activity in original regions[105-108]. Nonetheless, since cognition is supported on more diffuse networks, other phenomena may come into play, such as remote depression of function in non-injured tissue[109,110]. At the molecular level, the biological mechanisms that support these adaptive responses evolve over time after stroke onset and include growth-promoting gene expression, which explains axonal sprouting and focal changes as well as growth factor production and diffusion of molecular mediators, which explain diffuse parenchymal responses to damage[111-114]. To some extent, many of these mechanisms recapitulate early stages of development and their successful modulation and reconditioning to adult patterns may be associated with recovery[112].

It is possible, as supported by clinical and functional imaging data, to modulate naturally occurring adaptive responses through restorative and rehabilitation poststroke therapies[115]. Some of the events that occur during interventions are similar to those that correspond to successful spontaneous recovery, such as resuming back to normal patterns of recruitment and laterality[101,116]. Other phenomena seem to occur specifically in response to intervention exposure, but their significance is less well understood (e.g., adaptive vs maladaptive plasticity), such as new projections of neurons to denervated areas of the midbrain and spinal cord or the direction of cortical somatotopic map migration[6,57].

In stroke and other injury models like trauma, almost all patients show some kind of spontaneous neurological recovery, usually following a natural logarithmic pattern[18]. The recovery rate peaks in the first months poststroke, after which it progressively reaches a plateau supporting the idea for different mechanisms operating in limited time-windows[117,118]. Some of the mechanisms that underlie this process are non-learning dependent (e.g., salvation of the penumbra, spontaneous neuroplasticity, alleviation of diaschisis or revascularization through angiogenesis), while others are learning dependent (hebbian-type synaptic strengthening and pruning)[119]. Both these processes underlie skill reacquisition after stroke and can be amenable to modulation[119].

Besides stroke, adaptive brain neuroplastic responses have also been reported in traumatic brain injury[109,120,121] as well as in spinal cord injury[122-125]. The identification of similar plasticity mechanisms across such diverse forms of nervous system injury suggests that plasticity, as well as development and ontogeny, uses a limited biological repertoire of events across numerous contexts[6,112].

Psychiatric disorders

Brain plasticity in several psychiatric disease models shares much of the mechanisms found in the setting of central nervous system injury, such as stroke, but also reveals a number of noteworthy differences if the aim is a global understanding of neuroplasticity in humans[6]. In mental and addictive disorders, the mechanisms of neuroplasticity must be understood as therapeutic opportunities but, at the same time, as intimately related with disease pathogenesis. Clinical manifestations are the result of changes in key neural systems that support thoughts, emotion and complex behaviors[126,127], and are associated with polygenic risk factors and neurodevelopmental experiences in specific time-windows throughout life (e.g., stress, substance use, psychological trauma and social attachments)[128,129]. The natural course of disease is usually progressive, like neurodegenerative diseases, and the illness evolves by recurring bursts of activity, with high relapse rates. Each relapse increases the likelihood of the next episode or disease progression (sensitization theory) and recovery is slow and usually incomplete[130,131]. These types of diseases are associated with specific neuropathological processes and dysfunctions. They do not result from acute, usually circumscribed lesions, as happens in trauma and stroke, but are a consequence of insidious diffuse abnormalities in the limbic,

prefrontal and frontostriatal circuits, which support motivation, perception, cognition, behavior, social interaction and emotions[132,133].

The prefrontal cortical association areas are particularly important in relation to clinical expression of neuropsychiatric disorders. These areas are late to myelinate[134,135], highly plastic and extremely modifiable by individual cognitive and affective experiences [136,137]. They play a central role in many of the neurodevelopmental experiences, as well as in social cognition, decision appraisal and impulse control[135]. At a cellular level, prefrontal cortical neurons were shown to have synaptic plasticity and lasting changes in activity associated with different cognitive processes[137]. Disturbances in dorsolateral prefrontal networks are characteristic of schizophrenia and may be related to the disease activity or reflect developmental plastic changes[138]. Additionally, several genes associated with the risk of developing schizophrenia (DISC-1, dysbindin, brain-derived neurotrophic factor and the N-methyl-D-aspartate receptor) have been identified as playing a role in modulating neuroplasticity and patterns of cortical connectivity[139].

A striking model of maladaptive plasticity in psychiatry can be found in the addictive disorders[140]. Drug abuse includes several rigid and stereotyped behaviors that are supported in subcortical reward circuits. Their development is progressive, highly resistant to reversal and prevents the creation of new behaviors to compete with drug seeking[141,142]. As a result, the regulation of subcortical limbic and frontostriatal neural circuits by the prefrontal cortex is disrupted[143-145]. Prefrontal control mechanisms are excluded by subcortical reward systems, leaving drug abuse behaviors under the control of evolutionarily older regions that execute standard fixed responses to environmental stimuli[141]. At a cellular level, these particular neuroplastic changes are supported by phenomena such as loss of glutamate homeostasis in the nucleus accumbens combined with loss of synaptic plasticity in striatal spiny neurons, which in turn modulate perisynaptic metabotropic glutamate receptors[146]. These are critical for such neurophysiological processes as long-term potentiation and long-term depression[146]. Maladaptive plasticity can also occur in neuropsychiatric disease as a consequence of therapy, as is evidenced by tardive dyskinesia, associated with several antipsychotic medications[6].

Some plastic changes occur in response to therapeutic interventions in psychiatric and addictive illnesses[133]. Cognitive remediation and social skills training over 2 years in early schizophrenia were accompanied by grey matter increases in left hippocampus and left amygdala, in correlation with the degree of improved cognition[147]. Deep brain stimulation can reverse the symptoms of severe treatment-resistant depression and is associated with plasticity in limbic and cortical sites[148]. Sustained alcohol abstinence was linked to improved frontal white matter integrity[149]. Hippocampal neurogenesis has been demonstrated in animal models exposed to antidepressant medications, electroconvulsive therapy and stress reduction techniques, such as exercises and environmental enrichment [150]. All these findings taken together suggest that the successful treatment of mental disorders is supported on neuroplastic properties of the central nervous system at a cellular and molecular level but also in the structure and functioning of frontal–subcortical neural systems[6].

Neurodegenerative diseases and ageing

Neurodegenerative diseases that affect the brain are accompanied by a progressive decline in cognitive, behavior and motor functions. In the early stages of neurodegenerative diseases, neuroplastic changes occur and may represent pathogenic or correspond to compensatory responses[151-153]. Some molecules, like amyloid-beta dimers, have been shown to directly interfere with plasticity at a synaptic level[154,155]. Furthermore, with progression of the disease and the increase in pathological changes, some initially compensatory mechanisms may become pathogenic, leading to death of vulnerable neurons and disruption of networks[152]. In the early stages of Alzheimer's disease there is an increased response of the association cortices, reflecting a compensation for the impairment in transmissions from processing centers in primary cortical areas[156]. Over time, this process may lead to excitotoxic mechanisms, early neuronal death and functional consequences[157,158], with similar mechanisms having been advocated in Huntington's disease[159,160]. The distinction between compensatory and pathogenic plasticity of brain networks may be important for future treatment research because some changes are reversible and their normalization may prevent ongoing neuronal loss[152].

All changes attributable to the most frequent neurodegenerative diseases are usually superimposed on the normal ageing process[72,161-163]. Age-related changes include reduction

of plasticity through alteration of cellular functions, genetic control of axonal sprouting after injury, white matter integrity, brain volume and regional activation patterns[164,165]. These changes always come at a functional cost leading to a reduction in processing speed, working memory and sensory afferent processing. Currently, it is difficult to ascertain whether these changes are totally attributable to adverse physiological disturbances or the result of reduced engagement in cognitively demanding tasks and stimulating activities throughout life[162,163]. It is probable that both factors contribute to the normal ageing process, thus reinforcing the importance of studying preventive interventions aimed at maintaining brain plasticity. Furthermore, differences in age-related plasticity and cognitive reserve may explain the differential functional effects and vulnerability observed in patients with similar pathological degrees of Alzheimer's disease[165,166]. Comparable phenomena have been reported in other models of neurodegeneration such as multiple sclerosis[167] and vascular dementia[168].

These aspects must be taken into consideration in the long term management of people with prior nervous system injury from stroke, trauma or cerebral palsy as they age. Their experience and activity induced plasticity, which led to early improvements in daily functioning, may decline faster due to even modest deterioration in networks which retain less cognitive reserve, in contrast with those of normal healthy people[6].

c) Cognitive and motor intervention

Therapeutic interventions, such as cognitive or motor training, share many of the background neuroplastic mechanisms and have similar operative principles across several diseases[57]. In addition, in most neurologic and psychiatric disorders, disability results primarily from varied combinations of behavioral, cognitive and motor deficits. For example, if we think of patients with schizophrenia, they have predominant behavior impairments, but also important cognitive deficits amenable to specific interventions and even motor and extrapyramidal dysfunction later on the disease course[133,169]. In stroke or traumatic brain injury patients, motor and cognitive deficits are equally important, and the presence of certain types of behavioral disturbances are always observed (e.g., depression, anxiety, lack of motivation and sedentarism)[24,54,170,171]. It is also known that salience, motivation and attention can be critical modulators of plasticity[172-174]. The rule is that they coexist in individual patients and have the potential to cause serious impediment to the

rehabilitation process[6,175]. To match the right patient with the proper training approach all these aspects must be taken into consideration in the design of therapeutic plans.

New rehabilitation strategies usually aim at combining plasticity-inducing with plasticity-modulating interventions. To achieve these goals, interventions must first and foremost occur in a timely manner, usually early after injury (stroke or traumatic brain injury) or disease onset (multiple sclerosis or dementia), at an adequate intensity and over extended periods of time, to achieve long-lasting remodelling of neural circuits[54]. Once these requisites have been assured, the promotion of brain plasticity may be achieved through several strategies that have been proved beneficial in harnessing neuroplasticity. These can be pharmacological or nonpharmacological such as constraint induced therapy, skills training (cognitive, motor or behavioral), aerobic exercise, transcranial magnetic stimulation or deep brain stimulation interventions[6]. Finally, since plasticity is an experience-dependent phenomenon, besides its induction, optimal quality of training during the duration of the programs is a necessary condition to achieve good outcomes[47,48,176]. Only in this way it will be possible to harness neuroplasticity on one side and to modulate the cognitive, behavioral and motor results of intensive training on the other[6].

Much of the research and development activities in this field are focused on cognitive and motor training strategies. These are essential components of the majority of neurorehabilitation programs and deserve further comment here.

Cognitive training

If we consider the non-motor aspects of the human brain, cognitive training must be understood in a similar manner as physical therapy for motor deficits. Despite the continuum between cognitive, behavioral and motor functions, the former are more complex and supported on memory and other distributed neural systems, which presents specific challenges for the design of effective interventions[6]. The ultimate goal of cognitive training is to improve behavior through carefully designed exercises that stimulate neuroplastic changes in dysfunctional neural systems and modulate adaptive changes[6,177].

These approaches have a broad set of applications. They may be useful as part of the rehabilitation programs of patients with focal brain injury, such as stroke or trauma, where

multiple cognitive syndromes exist with few therapeutic options. In addition, they can also be applied to the treatment of other neurological and psychiatric diseases like multiple sclerosis, Parkinson's disease, early dementia, depression, schizophrenia or addiction. In the future they may even be combined with specific pharmacological and cellular based therapies to modulate their effect on promoting neuroplastic brain properties[59,73,178].

One of the first pieces of evidence for effective cognitive training has come from depression and anxiety disorders, for which there is a long history of cognitive-behavior therapies. The main focus of these treatments is the identification and modification of responses to maladaptive cognition, affect and behavior[179,180]. When individuals succeeded in modifying cognitive representations and behavioral responses to distressing stimuli, long lasting neuroplastic changes in the activation patterns of frontal and limbic systems were shown[181-183]. Another example of successful neuroscience-driven approaches to cognitive deficits can be found in the treatment of schizophrenia. It is well known that verbal learning and memory deficits are associated with disease progression and do not respond to pharmacological treatments currently available[169]. Computerized cognitive training focused on auditory and verbal processing was shown to improve verbal encoding and memory in a double-blind randomized controlled trial[184]. Similar training approaches, in combination with pharmacological treatment, have been tried to reinforce frontostriatal connections in addiction disorders[185].

The effects of cognitive training on specific neural systems were further evidenced by advanced functional brain imaging techniques in several psychiatric[186,187] and neurological diseases[59]. Modifications of functional MRI brain activation patterns in response to targeted training have been shown to correlate with important clinical and functional improvement in diseases like schizophrenia[183,188], dyslexia[189] and depression[183]. Furthermore, molecular changes in the density of cortical dopamine D1 receptors on PET scanning have been shown in normal subjects in response to cognitive training[190]. Real-time functional imaging is even being studied as feedback to orient meaningful behavioral changes[6].

Neuroscience informed cognitive training appears to be a promising therapeutic approach for a number of brain disorders. A key direction for this field will be to maximize the extent to which cognitive training in one domain generalizes to others, and the extent to

which such training has a meaningful impact on real-world functioning as well as the subjective experience of the individual[191]. Most noteworthy for the future is that the need to adapt and target, but mostly to control and monitor, cognitive training during the rehabilitation of individuals is becoming increasingly important. The effects of training over specific neural circuits and their strengthening must be coupled with significant behavior and functional outcomes. This requires large scale trials in several disease models and closely monitored interventions[58].

Motor training

Motor deficits may result following injury or through the action of diseases that affect the brain or spinal cord. In this context, several physical rehabilitation interventions were shown to improve the odds of a good functional outcome[47,192]. In this respect, stroke rehabilitation is a growing field of research and has provided us with good examples of interventions that have led to improved recovery after ischemic brain damage[18].

The higher levels of evidence for motor therapeutic techniques exist for constraint-induced movement therapy (forced use) for the arm and hand[193], body weight-supported treadmill training[194,195], bilateral arm training[196], task-oriented physical therapy[197], rhythmic acoustic stimulation[198], mental imagery (observation and imitation)[199,200], modulation of sensory inputs[94], functional electric stimulation[201] and more technology based interventions like robot assisted training[202-205]. Other practice strategies include increased repetition, variable demand and intensity levels[206], blocked versus intermittent practice sensory priming, contextual interference, modulation of attentional valence and reward, visualization, and various forms of feedback[6,192,207]. Similarly to cognitive training, functional neuroimaging studies have provided evidence of long lasting neuroplastic changes induced by motor training. One such example is constraint-induced movement therapy of the upper limb, which was associated with enlargement of the hand motor cortex map[208] and the bilateral sensorimotor grey matter[209].

There is a trend for motor training strategies to progressively incorporate technologies and becoming more complex, as is the case with robotic devices, treadmill locomotor training and body weight-supported techniques[46]. However, the incorporation of robotic devices has generally not been shown to improve outcomes more significantly than good quality

conventional therapies (task training and strengthening) in robust clinical trials which have focused on the optimization of activity dependent plasticity[192,210,211].

Intimately related with motor training is aerobic exercise, perceived as an extension of activity-based therapies and critical to plasticity promotion and counteracting the effects of sedentarism[171]. Several data support the benefit of its use for promoting plasticity and improving brain function in several diseases and during normal development and ageing[212-214]. Aerobic exercise programs, even for a few months, have significantly improved cognitive functioning in healthy ageing, early dementia, Parkinson disease and schizophrenia[214,215]. Furthermore neuroimaging studies have revealed its ability to increase brain volume in diseases such as dementia and schizophrenia[216,217] and to enhance brain network functioning [215,217,218].

Further research is needed to better understand how all these physical rehabilitation therapies can be optimized and coordinated with other forms of therapy such as pharmacological and behavioural treatments, especially across diverse patient groups with varied functional limitations[6,192].

4. Vision

All the work developed for this thesis, in the fields of cognitive and motor rehabilitation, is supported on a common vision and motivational drive. Training, either cognitive or motor, must be considered as a continuum for the majority of conditions that affect the human nervous system. The future of neurorehabilitation will depend on the ability to deliver very specific interventions and to properly measure exposure, learning effects and outcomes along complex multidisciplinary rehabilitation programs. For that purpose new neuroscience-driven technological tools are needed. Their design must be aligned with current and future needs of professionals, patients and families. Most importantly, it must follow the principles and scientific knowledge built upon decades of research on how to harness plasticity mechanisms in the human brain[73,93,192,219].

a) Concept model

Following neurological and psychiatric diseases, cognitive and motor training are so demanding and intertwined that future rehabilitation approaches will need to be increasingly considered together. For that to be feasible, new sensible technological tools need to be developed and tested. Cognitive and motor rehabilitation share the same neurophysiological substrate - the human brain and its nervous systems, networks, circuits, learning mechanisms and neurons[47,54]. They are so intertwined together that almost every single patient has a combination of both cognitive and motor deficits, irrespective of the underlying disease. Additionally, they share the same responses to injury, neuroplastic properties and principles of therapeutic interventions[192]. Current cognitive and motor training approaches are centered on the promotion of neuroplasticity and its modulation through controlled training and learning[73].

Both tools developed in this work, COGWEB (articles I – III) and SWORD (articles IV – VI), follow the same principles and share the same goal: to shift the therapeutic footprint from institution-based settings to community- or home-based environments, while at the same time maintaining specialized supervision of all training activities.

The starting point is the conventional relationship between a therapist and an individual patient. The therapist, being a physician, psychologist, physiotherapist, language or occupational therapist, starts their work by assessing the patient and establishing a plan.

The training plan is then transmitted to the patient in the form of a therapeutic prescription. Nowadays, most of the training activities, either cognitive or motor, are performed, under supervision, according to the prescription at an institutional environment. Home-based activities represent less than 10% of training and are hardly monitored[27]. All the monitoring of the execution of the training plan and its results are largely dependent on the availability and personal skills of the therapist.

In this context, through the well-reasoned application of information technologies, the aim would be to develop a professional web interface, where the therapist could record the baseline patient assessment and then prescribe a specific training plan, as well as remotely control all aspects of its execution by the patient: adherence, intensity, quality and learning progression.

For the patient, a similar web interface would provide home-based training activities and real-time feedback online. For cognitive training, an assortment of specific computerized exercises in a progressive computer game format, focusing on several important cognitive functions, would be the backbone of the therapeutic interventions. For motor training, it would be necessary to develop a complementary hardware interface capable to characterize 3D movement and deliver proprioceptive feedback on the quality of the task performed. This combination of web-based software and wearable hardware, which would enable the definition of an assortment of motor training tasks for the upper and lower limbs, could allow the prescription and monitoring by the therapist through its web console.

Besides the above mentioned requisites, the technology developed would have to be affordable and contribute to the sustainability of future health systems, so that, unlike many technological applications in the rehabilitation field (e.g., neuroprosthesis, brain-computer interfaces or robots), it could easily be implemented and become accessible to the vast majority of patients who need it[51,210,211].

Another conceptual principle concerned the contribution to contemporary translational networks in neurosciences[220,221]. For that reason both systems would need to function as investigation tools and be compliant with the concept of collaborative professional networks (explored in article III), to foster multicenter research projects, clinical trials and data sharing[222].

b) Technology: software and devices

The exploration of the concept model required two research and development pathways, which evolved in parallel. The first was dedicated to cognitive training and led to the design of the COGWEB system (articles I – II), while the other focused on motor training and originated the SWORD system (articles IV – VI). Both solutions benefited from the current emergence of telemedicine and telecare, together with public dissemination of technology (internet, information technologies, light, wireless and wearable computers and sensors, movement quantification tools and intelligent garment).

COGWEB – Web-based cognitive training

This system was based on an information technology health application. It combined an assortment of computerized exercises in computer game format, each focusing on specific cognitive domains, with a web-based platform that allowed the therapist to prescribe and monitor cognitive training sessions and the patient to perform them in more comfortable environments (e.g., home or community institutions). The system would also include a set of exercise books to be used in transition strategies and to stimulate daily training routines (articles I and II). The full mature expression of this system would be attained by the construction of a collaborative network dedicated to cognitive training (article III).

SWORD – Stroke wearable operative rehabilitation device

This system would include an operative information technology platform with similar characteristics to the one used for COGWEB, namely the professional prescription of training sessions, patient access at home, remotely supervised training and collaborative network functioning, all of which were performed online (article VI). However, instead of computerized games, an assortment of motor training tasks would be defined in collaboration with well experienced stroke rehabilitation medicine physicians (article VI). All these tasks may then be prescribed, but will need individual parameterization for each patient. To achieve this goal, a wearable vectorial 3D movement characterization device would be assembled from scratch, able to characterize movement performed by the patient. At the same time it would allow the analysis of its quality and provide immediate feedback to the patient, either through proprioceptive vibratory feedback or visual or audio feedback through the patient web console (articles IV and V).

c) Specific neurorehabilitation contents

In spite of all the technological developments required to attain success, the backbone of both systems would rely on very specialized and specific training tools. These would be designed and re-designed in collaboration with professionals who had years of experience supervising cognitive and motor rehabilitation programs in neurological patients.

The computerized cognitive training exercises

These would be developed from a set of 60 original exercises previously developed on pen and paper format and used extensively over more than 5 years in a memory clinic setting. The computerized exercises would share a number of characteristics, described in full detail in the COGWEB Manuals[223,224] and article I. The most important of these would include: the computer game format, progressing automatically between levels of difficulty, with immediate qualitative feedback to the patient; and each exercise focusing on specific cognitive domains to allow controlled interventions and detailed research protocols across several disease models.

The motor training tasks for the upper and lower limb

Most of the effort during the development strategy of the SWORD device focused on the development of a proficient movement characterization system and on the complementary vibratory feedback interface (articles IV and V). For the initial validation studies a simple task derived from the common hand-to-mouth task described in article VI would be isolated. These types of tasks would pertain to a global set of motor training tasks for the upper and lower limbs. Their specifications would be achieved through meetings convening expert stroke neurologists, stroke rehabilitation physicians, physiotherapists, occupational therapists and electronic engineers working in the area of software, network and hardware design. In a similar manner to cognitive exercises, these activities in their mature form (not part of this thesis) would progress through levels of difficulty automatically and provide immediate feedback to avoid repetition of error and optimize motor relearning. Nonetheless, all tasks should have to be initially parameterized to the level of performance of the individual. As a whole, the assortment of tasks designed, would provide a varied training environment. This will be set as the background for future clinical trials and the design of rehabilitation programs that incorporate motor training components utilizing the SWORD system.

5. Research pathways and questions

Taking into consideration the principles laid down in the state of the art and the vision explored in this thesis, the following research questions and hypotheses were assumed:

a) Cognitive training pathway

1- Is it possible to develop a system that may improve the overall quality of cognitive training interventions as well as patient access to this type of treatment?
    a) What is the adherence of patients with cognitive impairment and overall treatment intensity obtained through the use of such a system?

2- Is it viable to develop a collaborative network in the field of cognitive training with the potential to develop future multicenter research and foster translational processes in the field?

b) Motor training pathway

3- Is it feasible to develop a system that may improve the overall quality of motor training interventions, while at the same time, extending patient access to this type of treatment?
    a) To what extent is it tolerable to deliver targeted vibratory stimuli through a wearable device in stroke patients?
    b) Is a wearable device able to automatically reproduce the movement characterization obtainable through a conventional motor assessment scale like the Wolf Motor Function Test (WMFT)?
    c) Can the quality of motor task performance be improved through a device that combines 3D motion analysis with targeted vibratory feedback?

These questions are dealt with in the six articles that comprise the following section. The first three articles concern COGWEB development, the issues of usability and quality of training (articles I and II) and functioning of a multicenter cognitive training network (article III). Articles IV through VI concern the process of development of the SWORD system, starting with the tolerability of vibratory feedback, moving on to the validation of the 3D characterization device in a real world clinical setting and finally conducting the first in-hospital clinical trial focused on the quality of the task performed in a hypothetical first motor training session.

Part II – Experimental work

Cognitive training

Article I – A rehabilitation tool designed for intensive web-based cognitive training: description and usability study

Article II – Web-based cognitive training: patient adherence and intensity of treatment in an outpatient memory clinic

Article III – Implementation and outcomes of a collaborative multi-center network aimed at web-based cognitive training – COGWEB network

Motor training

Article IV – The vibratory stimulus as a neurorehabilitation tool for stroke patients: proof of concept and tolerability test

Article V – A novel system for automatic classification of upper limb motor function after stroke: an exploratory study

Article VI – Motor task performance under vibratory feedback early poststroke: single center, randomized, cross-over, controled clinical trial

Cognitive training

Article I – **A rehabilitation tool designed for intensive web-based cognitive training: description and usability study**

Cruz VT, Pais J, Bento V, Mateus C, Colunas M, Alves I, Coutinho P, Rocha NP

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Original Paper

A Rehabilitation Tool Designed for Intensive Web-Based Cognitive Training: Description and Usability Study

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Abstract

Background: Cognitive deficits are among the most disabling of neurological diseases and have a serious impact on the quality of life of patients and families. Cognitive training has been proven successful in improving or compensating for neuropsychological deficits after acute brain injury, but its efficacy highly depends on the intensity of treatment over an extended period of time. Therefore, cognitive training indicates expensive human resources and renders the rehabilitation process vulnerable to physical and economic barriers for the majority of patients.

Objective: The aim of this study was to develop and test a new Web-based rehabilitation tool that provides intensive cognitive training at home under clinical prescription and monitoring, at affordable costs.

Methods: From a pool of 60 original exercises, designed and used over the past 10 years for cognitive training at our center, we developed 27 exercises on a computer game format, with automatic increase or decrease of difficulty levels. These exercises were assembled in a clean, user-friendly design and covered various cognitive domains such as attention (n=4), memory (n=11), language (n=3), calculus (n=3), praxis (n=2), and executive functions (n=3). A Web 2.0 platform was also designed to provide medical prescription of cognitive training sessions, performed at the patient's home. These sessions included continuous monitoring of compliance, performance, and evolution; algorithms for automatic adjustment and long-term learning through use, and database recording of all activities. The end-user interaction test included 80 patients from our memory clinic from several groups including subjective memory complaints (n=20), traumatic brain injury (n=20), stroke and other static brain lesions (n=20), and mild Alzheimer's disease (n=20). During a 1-hour session, patients and their relatives were taught to use the system and allowed to practice using it. At the end of the session, they were asked to complete a questionnaire.

Results: A total of 48/80 patients (60%) attended the training session. The mean age of the patients was 60 years (SD 13.3, range 41-78), and the mean level of formal education was 6 years (range 4-16). Of all the participants, 32/48 patients (66%) have previously used a computer. All patients and their relatives made a positive evaluation of the cognitive training tool. Only 2/48 patients (4%) were not interested in performing the exercises at home; 19/48 patients (39%) mentioned the need for further coaching from a relative or health care professional. The patients who mentioned difficulties in performing the exercises have not used the computer earlier.

Conclusions: This new Web-based system was very well accepted by patients and their relatives, who showed high levels of motivation to use it on a daily basis at home. The simplicity of its use and comfort were especially outlined. This tool will have

an important effect on human resource management, in increasing the patient access to specialized health care and improving the quality and national health system costs of rehabilitation programs.

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KEYWORDS

cognitive training; cognitive deficits; neurorehabilitation; Web-based applications; eHealth systems; usability test

Introduction

Overview

Neurological disorders are commonly associated with a variety of cognitive and motor deficits that result in an ever increasing demand for health services. Among all major groups of diseases, neurological disorders constitute 6.3% of the global burden of diseases worldwide [1]. This value may be as high as 10.9% for high-income countries and 11.2% in the European region, which corresponds to 15-30 years of life lost adjusted for disability per 1000 inhabitants each year [1]. Irrespective of the cause (eg, stroke, brain injury, or dementia), people with cognitive impairments rarely recover spontaneously or completely [2].

Once established, brain damage is difficult to revert and pharmacological tools with a confirmed positive result are scarce [3-5]. The recovery process is typically slow, relies on the remaining plastic properties of brain tissue, and is highly dependent on complex and intensive assisted rehabilitation programs [6]. Similar to other rehabilitation processes, the results of the recovery process also depend on the timely onset, intensity, and specificity of the treatments [7,8].

The neurorehabilitation programs have proven efficacious in the compensation, improvement, and stabilization of cognitive deficits in several diseases and nosological models [9-17]. However, despite being accepted as a fundamental component of current treatment plans, these programs often impose strong restrictions on the patients' access to such treatments [18,19]. These programs commonly require multidisciplinary teams and are usually performed in hospital settings, away from the patient's home, in the presence of a relative (a huge effort by patients, families, and institutions). Classic cognitive training in particular requires pencil-and-paper tasks and object manipulation under specialized supervision. These characteristics result in a large economic burden to both the health system and families [20,21]. Furthermore, they limit the efficacy of the treatment by increasing the difficulty in coping with rehabilitation sessions in due time (soon after injury) and in attaining the high intensity of treatment necessary to foster nervous system plasticity [8,22].

The computer has emerged as a tool for the training and educating patients with brain injury, thus reducing the large demand for human resources and increasing the motivation of these patients [9,23]. However, the use of informatics programs in cognitive training is a recent approach; hence well-designed clinical trials are scarce, and the majority of them are inadequate for efficient integration in current clinical practice [18,24]. Therefore, the sole reliance on repeated exposure to computer-based tasks without some involvement and intervention by a therapist is not recommended [9].

To address these problems, we decided to develop a new integrative Web-based tool "COGWEB" for home-based cognitive training, centered not only on the patients' needs but also on professionals and institutional requests. This instrument takes advantage of the growing knowledge on computerized training protocols for cognitive rehabilitation [18,25-29] and combines a Web-based platform with computer exercises developed over the last few years in an outpatient memory clinic. The aim of this tool is to increase the quality and overall intensity of cognitive training programs.

This paper presents the main characteristics of the developed system and the results of a usability testing of the online system performed by patients suffering from highly prevalent neurological diseases, and their relatives.

Previous Approaches

Over the past few years, several solutions have been proposed to increase the availability of cognitive training. In fact, the market is flooded with commercial brain exercise programs that claim to improve cognition, have diagnostic abilities, and even replace the role of specialized health professionals along the way [30]. However, extensive clinical validation is still lacking and only a few programs have undergone scientific inquiry [26,27,31-33].

Previous approaches to cognitive training can be summarized into 3 categories: (1) cognitive domain-specific programs, (2) neuropsychological software programs, and (3) video games.

Cognitive domain-specific programs train specific cognitive capacities, usually under professional guidance at a health institution, and rely on the repetition of standardized tasks on a computer. Training of reaction time [34], processing speed [35], selective attention [36], and working memory [37,38] are some examples of these applications.

Neuropsychological software programs are designed to train several cognitive domains using a variety of tasks. These programs rely on immediate feedback and allow individuals to evolve based on their performance. Most studies with these tools analyze multiple cognitive domain interventions, either in the lab or remotely, for example, the Posit Science Brain Fitness Program [39], the Integrated Cognitive Stimulation and Training Program [40], the Neuropsychological Training [41], the CogniFit Personal Coach [42], and Lumosity [29]. Most of these programs are commercially available and especially designed for older people, as this age group is their biggest target market [30]. Nonetheless, there is a specific growing group dedicated to children and academic performance, usually under the format of tutorials [43].

Video games include computer or other electronic games where the players are enrolled in a set of activities oriented toward achieving a specific goal. Patients are given immediate feedback, and these games allow for an automatic progression between different levels of difficulty according to performance. The cognitive domains in this category are more difficult to individualize [18,44]. This category includes games originally designed to improve cognition like Nintendo's Big Brain Academy for Wii [45], classics like Pac Man, Donkey Kong, or Tetris that were studied for processing speed [46], and recent commercial successes like Rise of Nations [47] and Medal of Honor [48] that were assessed for attention, memory, executive function, and visuospatial abilities.

Unmet Needs and Problems

Computerized cognitive training offers several advantages over traditional pencil-and-paper tasks mediated by a psychologist or therapist at a health institution. The human resource costs per patient treated and the treatment time decrease, and home-bound or remotely located persons can have easier access to the treatment. In spite of all the available alternatives, several important needs remain unanswered [49]. Most of the programs available have a reductionist approach to brain conditioning or rehabilitation, discourage human relations in favor of self-executed exercises at home, and increase the distance between individuals or patients and specialized health professionals [30]. Furthermore, although all individuals may benefit from the use of novel technologies, the acquisition of regular training routines and computer skills is not straightforward for older people or patients with cognitive problems if we want to have an inclusive approach.

From the scientific point of view, research studies lack well-conducted randomized clinical trials, and most importantly, a clear definition of what a placebo is in these trials [50,51]. Furthermore, there is an absence of dose-finding studies that could assess what is necessary to obtain effects on other cognitive domains or improvement of daily living activities. Another major concern is the lack of studies to determine the possible side effects of these interventions. Noninvasive brain stimulation and cognitive enhancement strategies may have a mental cost on some abilities [52]. This feature is of utmost importance to deal with brain injury models like stroke or traumatic brain injury, where the rehabilitation of several brain functions competes for the uninjured cortex plastic and metabolic properties. Side effects are also important in neurodegenerative disease models where intensive training activities may have undesired effects if not controlled, monitored, or integrated in the social life and networks of individuals [30,44,49].

Methods

End-User Interaction Study Design

Clinical Settings for Using COGWEB

Patients with changes in cognition attend different specialized medical appointments, where their medical and therapeutic needs are identified and assessed. Normally in the diagnosis procedure, besides other examinations, the patient is frequently submitted to neuropsychological assessments. Therapeutic plans for cognitive intervention are defined in this multidisciplinary clinical environment. The COGWEB appears in this context as a work tool, and the practitioner is responsible to manage and use the system, according to the clinical context and the patient's characteristics (Figure 1, Table 1). The mandatory prerequisites for using the COGWEB are the existence of a medical diagnosis, a detailed neuropsychological characterization of the cognitive impairments, and a health professional willing to manage the treatment program, essential for a quality analysis of the system. The therapist that handles the system plays a central role in defining the degree of supervision and the type of patient exposure to the treatment and the Web-based system. The management of objectives, areas of cognitive intervention, individual composition of training sessions, and duration and intensity of treatment are all under the responsibility of the health professional. Although the presence of therapists is not continuously necessary for the training, they can actively direct all activities via online interaction and periodic (eg, daily, weekly, or monthly) meetings or telephone contact with the patient and caregiver (Multimedia Appendix 1).

Figure 1. Clinical context in which COGWEB was developed.

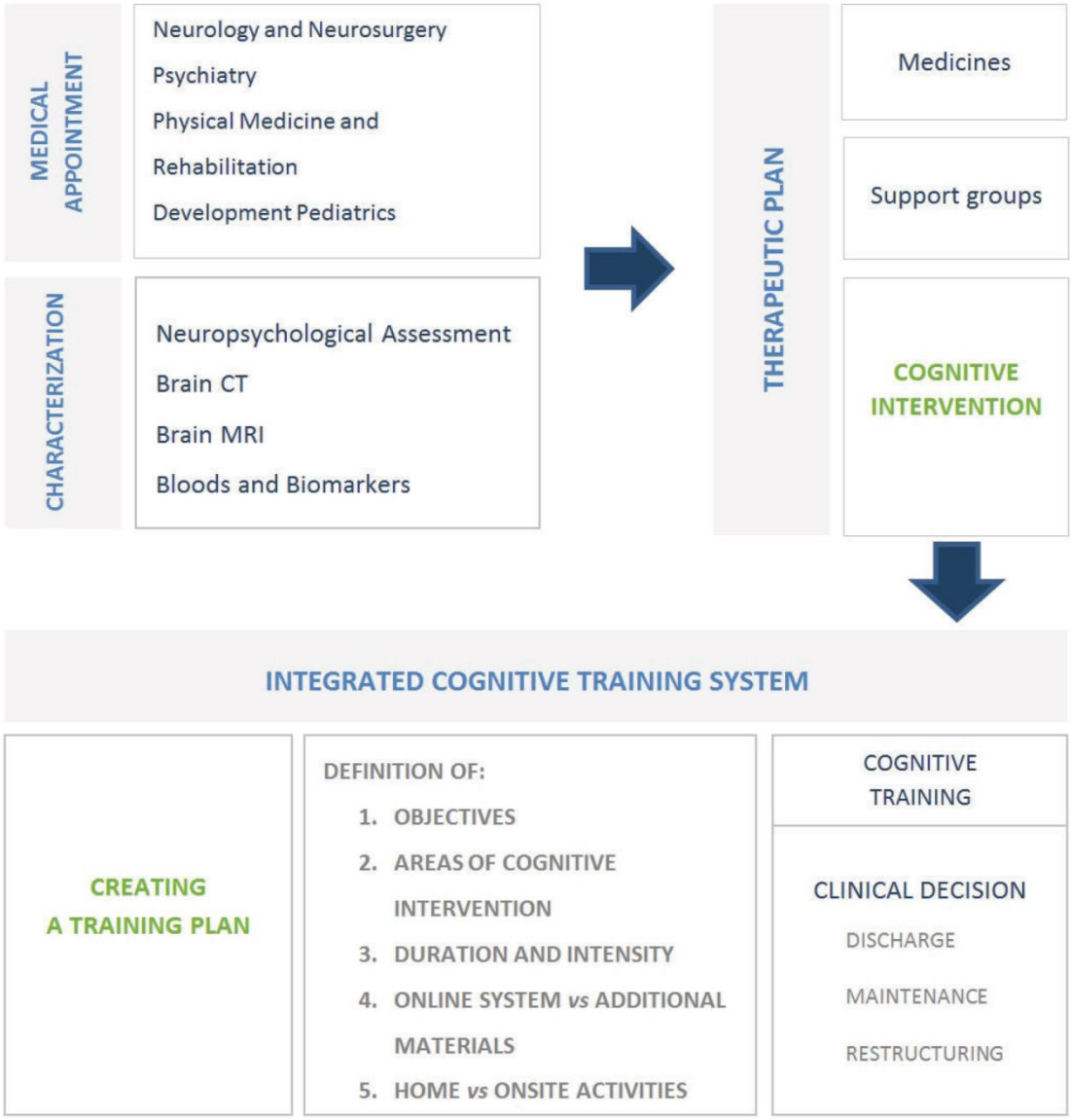


Table 1. Target neurological conditions of the COGWEB system.

Major subgroups of diseases	Most important diseases
Non progressive structural lesions	Traumatic brain injury
	Stroke
	Sequels of brain paralysis, anoxia, radiotherapy, encephalitis, brain surgery, and other static brain lesions
Neurodegenerative diseases at an initial stage	Mild cognitive impairment
	Alzheimer's disease
	Parkinson's disease
	Vascular dementia
Cognitive dysfunction of functional nature	Subjective memory complaints
	Depression
	Normal aging and active aging strategies
Other nosological models	Multiple sclerosis
	Schizophrenia
	Hyperactivity and attention deficit (adults and children)

Patient Selection

A group of 80 consecutive patients from our outpatient memory clinic were selected and grouped equally into 4 nosological groups: 20/80 (25%) with subjective memory complaints, 25% with traumatic brain injury, 25% with stroke and other static brain lesions, and 25% with mild Alzheimer's disease. The recruitment process took 3 months, and the following cumulative selection criteria were included: (1) a medical diagnosis compatible with 1 of the 4 groups, (2) 4 years of formal education completed, (3) favorable opinion of the attending neurologist, (4) no sensorial or physical deficiency preventing the use of regular computers unaided (eg, blindness, hemiplegia, or amputation), and (5) informed consent from both the patient and relative.

Group Sessions, Procedures, and Usability Questionnaire

Patients and caregivers (n≤20) were scheduled for psychoeducational group sessions at the hospital in a room with 10 computers with the Internet access. Two attempts per patient were performed to schedule the sessions at working hours. The sessions were structured into 3 parts (20 minutes each): (1) a psychologist provided an overview about the program and individual credentials for each patient to assess the online system; (2) the pair patient-caregiver was allowed to experiment with the program unaided on 1 of the 10 computers in the room; and (3) after completing a regular training session with 8 different exercises, an opinion questionnaire on the easiness of use and motivation for using it at home was answered anonymously by both the patient and caregiver in the absence of the psychologist (Table 2).

Table 2. Opinion questionnaire.

Question		Possible answers
Q1	Were the instructions easy to follow?	Yes/No
Q2	Were the exercises interesting to you?	Yes/No
Q3	Did you find the training useful to you?	Yes/No
Q4	Are you motivated to use it at home?	Yes/No
Q5	Having completed this training session, do you feel already independent to use it, or do you need additional training?	Independent/Additional training

Ethical Issues

All patients and caregivers understood the purpose of the study and provided written informed consent. An approval from the referring neurologist was also obtained to guarantee that patient and caregiver expectations were properly managed after the usability test. This study was approved by the hospital review board and ethics commission.

Rehabilitation Tool

Main Characteristics

The Integrated Cognitive Training System is composed of 2 components: (1) an online platform, COGWEB and (2) a series of tools in the classic format of exercise books [53,54].

First, the COGWEB allows for the implementation of personalized cognitive training programs remotely, in the patient's living environment. The tool is implemented through the professionally supervised prescription of exercise sessions,

in computer game format, targeted to various cognitive functions, such as attention, executive functions, memory, language, praxis, gnosis, and calculus. Supervision is conducted by specialized practitioners without the loss of human contact or management (Figure 2).

Second, the exercise books were designed in parallel with the online platform and are useful during the initial stages of the training (Table 3). They can also be used to switch between stimulation methodologies if deemed necessary by the health professional, and to help people who, for various reasons, have no regular access to the Internet. Thus, people who face difficulty in using computers can start their training activities with paper and pencil, acquire routines, and then move up to a more intensive system (Multimedia Appendix 2).

Both system components are meant to be used as support for a wide range of cognitive interventional approaches, or at distance, under supervision with the neuropsychologist, being more or less present depending on the case (Figure 1, Table 1). The main structure of the online system is described in Figure 2 and its principal functional characteristics, resulted from a set of usability requirements defined by a board of clinicians, and are explained in the following text.

The online system was structured for modular cognitive training, as exercises were grouped according to major cognitive function stimulated (Table 4). This system covers different degrees of impairment, from normal function to moderate deficits, given that all exercises have sequential levels of difficulty and were designed for use in a wide range of diseases and ages (Figure 3). The monitoring tools coupled with biostatistics and long-term system analysis tools and a storage system that records performance continuously are incorporated into the system to supervise clinical evolution and adjust programs according to the patients' progression. This system can be used in supervised group sessions with patients and can also be accessed at home or at any other place in the community with an Internet connection, only requiring a login information (without software installation or updates).

Figure 2. Global system scheme.

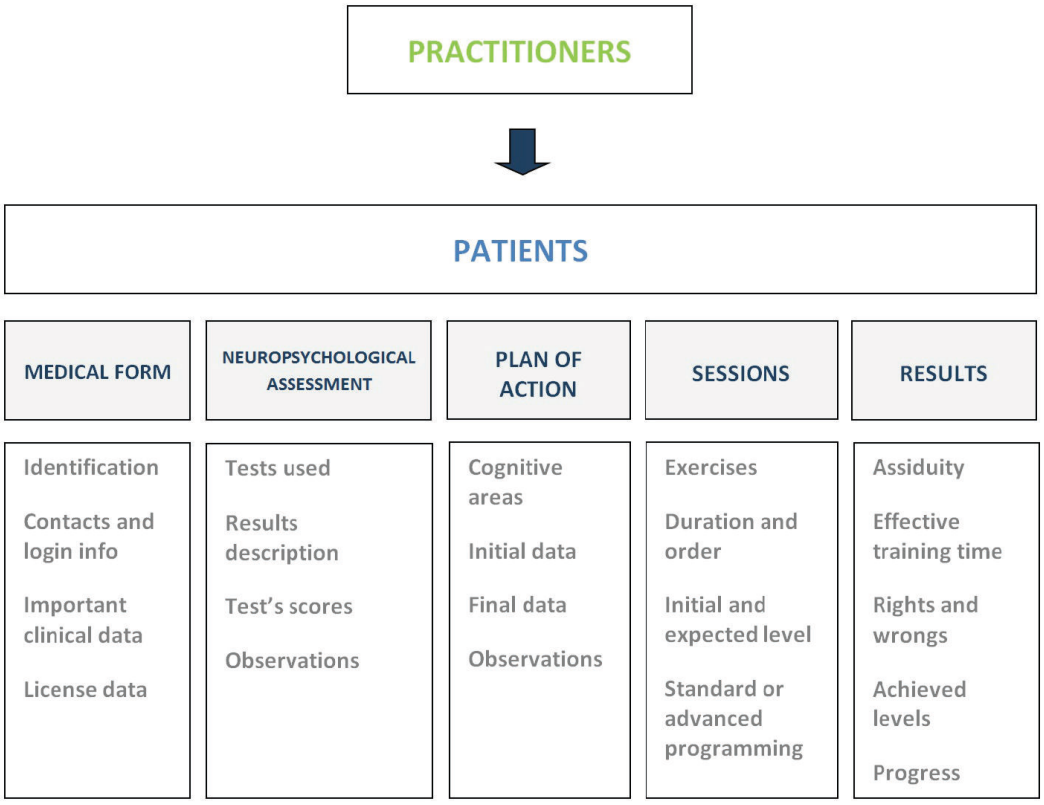


Table 3. Exercise books available and their target population.

Exercise books	Active ageing	Degenerative diseases			Static brain lesions	
		MCI[a]	Mild dementia	Moderate dementia	Stroke	TBI[b]
Weekly notebooks, Volumes I to IV	✓	✓	✓	✓	✓	✓
Monthly notebooks Level 3, Volumes I to III	✓	✓			✓	✓
Monthly notebooks Level 2, Volumes I to III			✓		✓	✓
Monthly notebooks Level 1, Volumes I to III				✓	✓	✓
COGWEB Art, 3D pieces	✓	✓	✓		✓	✓

[a]Mild cognitive impairment.

[b]Traumatic brain injury.

Table 4. Available exercises per cognitive domain.

Cognitive domain	Exercise	Levels (N)
Attention	Attention to the letter	5
	Attention to the number	5
	Find the letter	9
	Water colors	10
Memory	Attention to the news	3
	Fast eye	8
	Fast memory	8
	Long memory	14
	Numbers in order	8
	Restless cubes	7
	Reverse the stars	7
	Supermarket	8
	Who moved	7
	Worms	7
	Where were they	8
Language	Arrange the words	6
	Follow the orders	9
	Starts with	8
Executive functions	Match the color	3
	Contrary	7
	Inside or out	9
	Logic mind	9
Calculus	Fast mind	5
	Let's go shopping	3
	Mathematical table	6
Constructive capacity	Puzzles	6
	COGWEB Art	7

Figure 3. Examples of COGWEB exercises.

Online System Architecture

The medical system, accessible via Internet browser, was designed to meet the requirements of health professionals and patients. Both groups need specialized and usable interfaces to access the system and introduce daily inputs. All data are centralized, recorded, and acceded on a health record system. During the cognitive training sessions performed by the patient, all of the data is updated continuously in real time via Web-based system and is saved on a remote database that furnishes all required information to be examined by the health professional. The database contains information of all patients and health professionals, and maintains a record of all training programs prescribed and patient performance. The system also includes a biostatistics analysis framework of unidentified data generated by the users of the system. The main purpose of the system is to analyze the quality of processes according to the standards established by a board of consulting clinicians. All data used for this computation remain unidentified and cannot be linked to the professional or patient who generated it. This policy was set according to the strict demands of the National Commission for Data Protection, established in accordance with European regulations (Directive 95/46/EC) [55]. The results from these computational operations are used to assess the application quality of the system by health professionals, to perform benchmarks of clinical outcomes, and to aid in the long-term improvement and context adaptation of the system. Some changes occur automatically, according to machine learning algorithms based on the internal statistical analysis. These tools provide additional evidence for the substitution of a useless exercise, the changing of system features that lead to errors, setting new automatisms like alert signs for some clinical situations, or the preparation of specific educational campaigns for professionals.

Network Operations and Coworking

The system is designed to become accessible to a large number of people, through a network of centers and practitioners specialized in using it. Upon agreement by the professionals and patients, anonymous data on the treatments prescribed and clinical evolution are stored on a centralized application. The analysis of these data allows the depiction of the trends and the assessment of the quality of the tools and operative processes throughout the time. Thus, the system can be evolved and adapted to the needs of patients, professionals, and institutions. All agents can share useful information and guidelines on operational processes through a collaborative network. Furthermore, all neuropsychologists and practitioners who receive training on using the COGWEB system and share quality criteria in operating the system are stimulated to develop personal and team research projects. This step will improve the quality of the projects, increase the size of possible samples without incurring additional costs, and conduct multicenter trials while shortening the required time to complete them.

Professional Console

Overview

The health professionals can access the rehabilitation program by entering their username and password on the website [56]. The website, in addition to allowing access to the online training area, contains educational content targeting the general population and a blog. The aim of the site is to provide scientific

and pedagogical information about cognitive functioning and its changes, and the possibilities and indications for cognitive training [56].

The most important menu is the patient health record where the professional may add patient's information to the system and manage it later. The patient menu includes several submenus: medical form, neuropsychological assessment, intervention plans, session programming, and results.

Medical Form

In this submenu, 3 types of data can be inserted: (1) identification data, (2) clinical data, and (3) data on the duration of the license to use the system and patients' credentials to access it.

Neuropsychological Assessment

This menu, allowing the entry of neuropsychological assessment data on any patient, is organized into 2 parts. The first part records general descriptive data of the evaluation and the second part helps record each test and the quantitative results (preferably raw data) obtained in each neuropsychological test. Therefore, several evaluations can be recorded over time.

Intervention Plans

Health professionals can use this option to enter the general information of the treatment plan, like duration, main cognitive domains, and the expected intensity of training. This option allows to entering information on as many intervention plans as needed. The data entered in this section can be used for the detailed evaluation of the quality of the tasks prescribed to the patient in the next session. If a decision is made to train working memory or attention, the system provides information on all of the exercises the patient is prescribed, in addition to their duration.

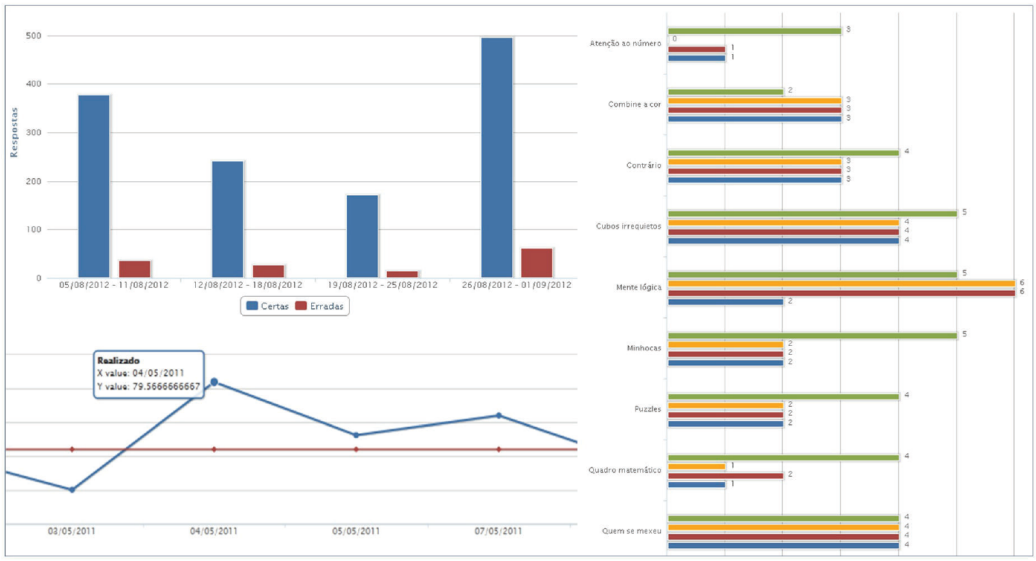
Session Programming

The prescription system provides 2 ways to create sessions: (1) the standard mode and (2) the advanced mode. These two work modes share a set of prescription parameters, and the planning of each session requires the following parameters: the selection of exercises, their starting and completion dates, their order of appearance, the duration of exposure to each exercise, and the initial level and the level expected to be achieved at the end of the plan. These two modes, however, differ in defining and managing the training schedule. The standard mode is a faster and simpler way to plan sessions in which the patient conducts the same set of exercises in consecutive days. In the advanced prescription mode, the prescribing health professionals select the day on which they want a specific session to be active and the intended activation period, that is, morning, afternoon, or all day. Thus, the needs that currently exist in sophisticated and intensive rehabilitation or cognitive training methodologies in specific areas can be met.

Results

The current system provides several kinds of progress graphs: right answers versus wrong answers, global training time (actual realized time vs planned time), game time in each exercise, concluded levels, accesses (realized accesses vs planned accesses), and a progress summary per exercise (expected performance vs real performance) (Figure 4).

Figure 4. Examples of progress graphs.



Patient Console

Overview

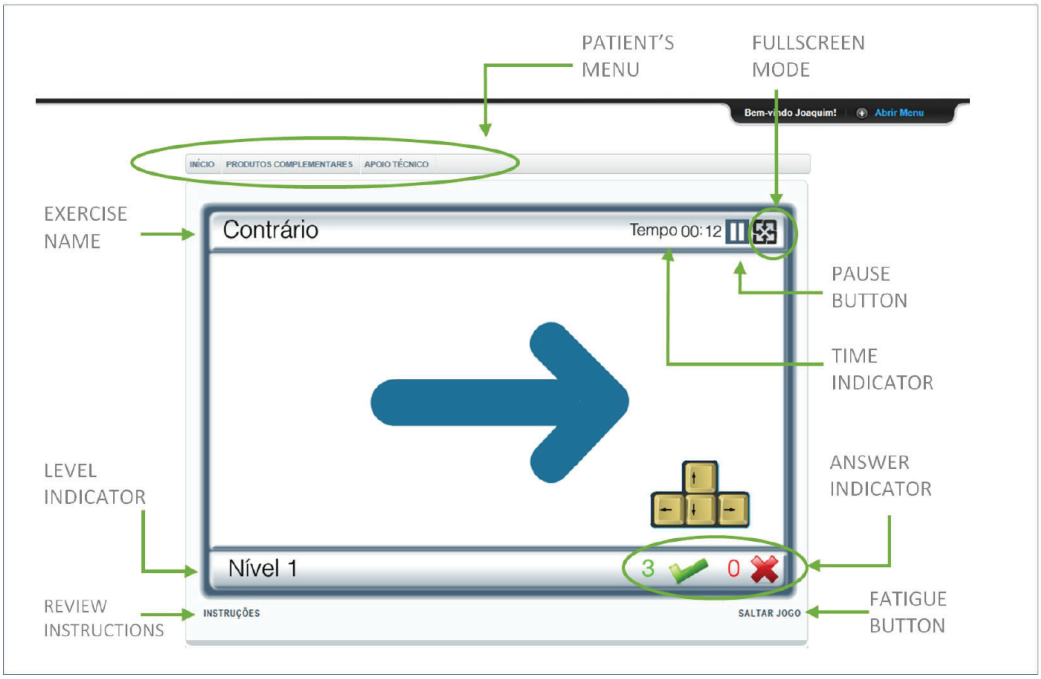
The COGWEB is accessed through the website, similar to the professional's login [56]. The entire login dynamic is identical in both the consoles with the only difference in the attributes and areas associated to the username/password.

Training Sessions

As soon as the patient credentials are introduced, the training session starts automatically. First, the patient views a welcome

screen with the training session information (number of exercises prescribed, total duration, and other general instructions) and a start button. When the patient feels ready, the first exercise planned starts, with no need for additional clicks or menu navigation. The simplicity of accessing the program eliminates the obstacles that may hinder training program compliance. The training arena is presented, by default, in a normal sized window. However, for added convenience during the exercise, the user can switch to full screen, by pressing the signed button (Figure 5).

Figure 5. Screen appearance of the patient training area and principal features of the game arena.



Game Arena

Each exercise starts with a set of instructions, written on the screen and spoken through the speakers, for 20 seconds before the onset of the exercise. Instructions can be viewed at any time, even during the exercise, by pressing the instructions button. After the instructions, the exercise starts and the game arena appears. However, as time is an important factor in some of the exercises (eg, trainings processing speed), it is crucial to guarantee the patient's attention to stimuli from the beginning. For that reason, there is a start button on the screen. The game arena is similar between various exercises making the learning and adaptation process easier. It comprises a central area, where the exercise takes place and the answers are given, with a frame around it. The exercise name is shown on the upper left hand corner of the frame, and the time remaining, the pause button, and the full screen activation button appear on the upper right hand corner. The lower left hand corner shows the level indicator and the bottom right the answer indicator (right and wrong) (Figure 5). The bottom of the screen displays 2 buttons: (1) the instructions button, which enables the patient to review the instructions even during the exercise and (2) the fatigue button (designated, skip game button), which can be activated if the patient feels tired or discouraged with a specific game.

The pause button allows the session to be stopped in case of unforeseen events that might distract the patient and hinder the performance. This button should be used exceptionally.

Motivation Tools

Upon successful completion of each level, a support message appears that is expressed simultaneously on the screen and in audio. When the performance by the end of the level does not fulfill the criteria for progression, the level is either maintained or decreased, depending on the progression rules for each game (see description of exercises). In this case, no information is given to the patient, the instructions for that level are just repeated, and the game continues. During the last exercise of each session, at the bottom of the game arena, the buttons that restart the session and end the session appear, which allow the patient to repeat the session, if they feel up to it, or end the session, in case they already feel fatigued. At the end of the session, this information is presented again.

Cognitive Exercises

Overview

The COGWEB system is composed of 27 independent exercises, distributed by different cognitive areas (Table 4). All exercises were first developed in a classic format including paper, pencil, cards, and other physical materials. Before being converted to the current computer game format, which took a period of more than 5 years, a pool of 60 original exercises were subject to

extensive clinical use, validation, and refinement at our outpatient memory clinic [53,54]. These exercises share some important characteristics.

Functional Organization

Each exercise is organized around the stimulation of a specific cognitive area. However, one exercise does not train only one area, as other additional areas are also involved in solving the tasks. This multiplicity of tasks is intimately related to the integrated function characteristics of the human cognition.

Levels of Difficulty

The exercises were developed to train various degrees of cognitive defects, from mild to more severe impairments. Exercise progression is automatic, by levels, becoming more difficult or easier in response to the patient's performance, both inside the same session or in consecutive sessions. The different degrees of difficulty, depending on each game, are obtained through manipulation of some of the features, either alone or in combination: the number of items per level, their complexity, and the interval between stimuli within the same level (game vs patient's paced rhythms). For choosing the stimuli for each exercise (words, figures), special attention was given to various aspects that contribute to the complexity of the items, such as the extension of words, their degree of imageability, semantic proximity, or, in the case of figures, the number of graphic elements or graphic composition.

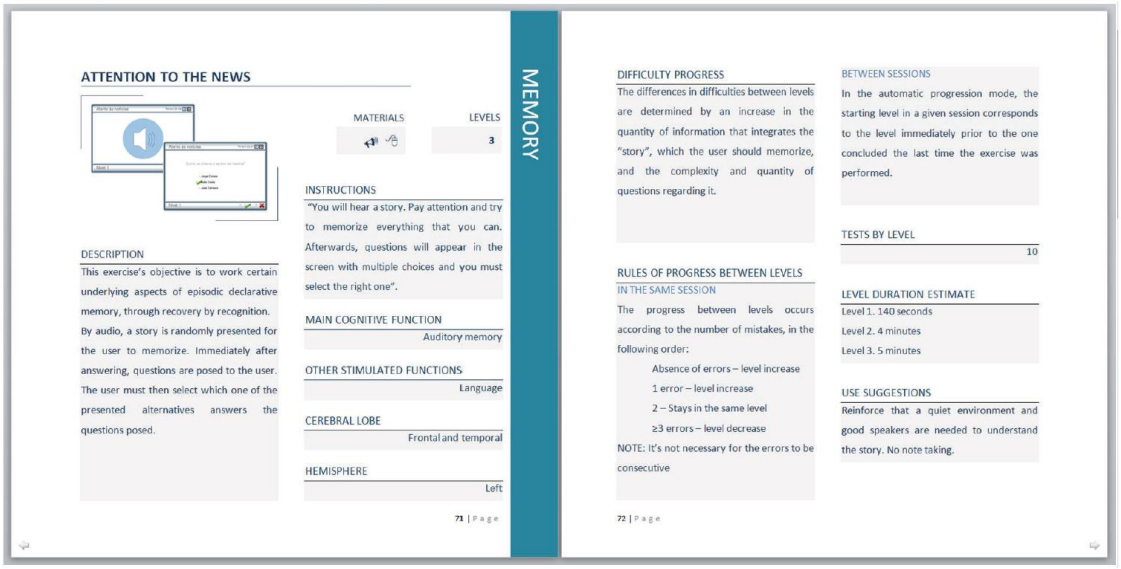
Random Stimuli

The structure of the exercises, at its base, is composed of sets of stimuli grouped by difficulty. On the same level of an exercise, the stimuli always appear in a random, nonsequential way to prevent memorization.

Information Sheets

For each exercise, the prescribing health professional has access to an individual sheet including the following parameters: general description, patient instructions, and multimedia requirements; main cognitive function that the game stimulates and other secondary stimulated functions; cortical areas recruited, according to anatomic-functional models of bibliographic basis; principles behind the choice of items that compose the game and the organization of their level of difficulty; the number of levels for each game, rules of progression between different levels and the number of tests in each level; estimated average time required for a normal individual to complete levels 1, 2, and 3 of each game (important for setting the minimum time of each game in sessions that might demand a level increase); and special use suggestions (Figure 6).

Figure 6. Example of an information sheet for the game exercise "Attention to the news".



Results

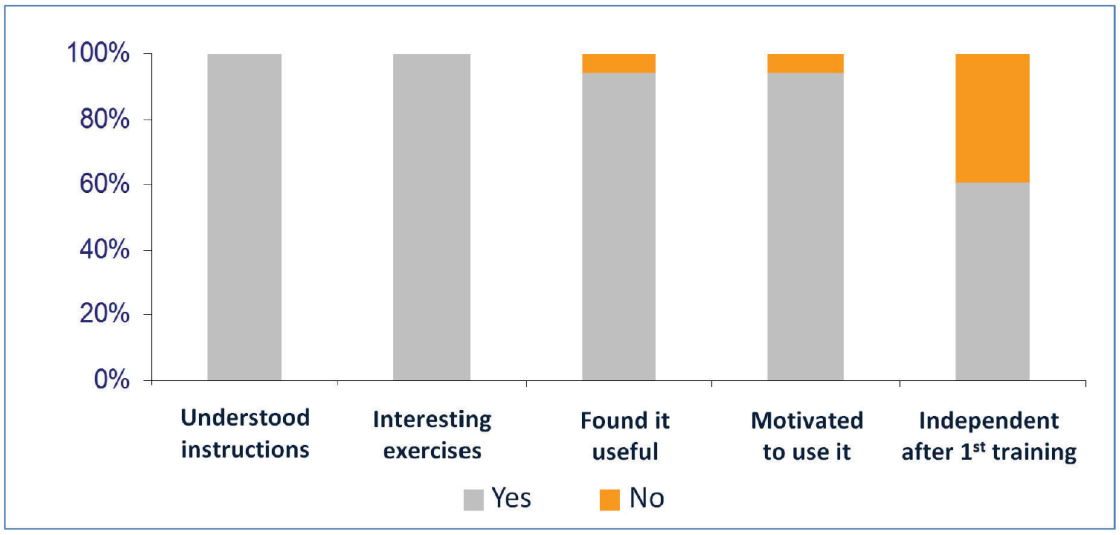
Of the 80 patients initially selected, 48 patients (60%) attended the psychoeducational group sessions and completed the usability test proposed. The mean age of the respondents was 60 years (SD 13.3, range 41-78). A total of 21/48 participants (44%) were female. The mean level of formal education was 6 years (SD 4.3, range 4-17). Previous use of the computer was shown by 32/48 patients (66%). Of all the participants, 32 patients (66%) did not complete the study because they were not able to attend the assessment sessions at the hospital. However, this did not differed between groups (P=.12).

As shown in Figure 7, all patients in the presence of their caregivers understood the instructions given in the training session and during the execution of the 8 different exercises (Q1). All patients found the exercises used in the training sessions interesting to them (Q2). Only 2 of the 48 participants (4%) did not find the exercises useful for their clinical condition (Q3). The same percentage of respondents was not motivated to use the system on their own at home (Q4). After the first

training session, 19/48 patients (39%) indicated the need for further help from the caregiver to use it at home (Q5).

In the group of patients that mentioned the need for additional training (n=19), 74% (14/19) were male, 79% (15/19) have not used the computer earlier, and 16% (3/19) had only sporadic exposure to computers.

Figure 7. Answers to the opinion questionnaire (Q1-5) (%).



Discussion

Principal Findings

This new system was very well received by patients and their relatives, who showed high levels of motivation to use it on a daily basis at home. The simplicity of its use and comfort were especially emphasized. Considering the mean age, the level of instruction, and the cognitive deficits of the patients enrolled, 19/48 patients (39%) required some kind of coaching to achieve independent use of the system. The formal evaluation of usability by both professionals and patients will be given further attention in future studies.

Optimized Approaches

Compared to most related technologies available [18,43], COGWEB characteristics were defined after thorough study of existing cognitive training procedures in an outpatient memory clinic. The improvement of the quality and access to treatment by the patient were very important. Nonetheless, the system has the rehabilitation professional at its core as is recommended [9]. Ultimately, it is a specialized working tool that improves health decision making and time management per patient treated. A significant part of cognitive interventions can be done outside the health care units, by maintaining high quality levels of therapy through bidirectional communication between patients and professionals thus avoiding isolation. This step promotes patient comfort and treatment adhesion while eliminating economical and geographical barriers [30,44,49]. The impact of several degrees of personal presence of the therapist on the overall quality of training and outcomes are currently being evaluated in a prospective study.

Another significant feature of the system is its suitability for coworking and multicenter use in collaborative networks of professionals and institutions. This will foster investigation in the field and position COGWEB as one of the most prepared tools designed for clinical trials in cognitive interventional approaches. In the field of neurorehabilitation, high-quality scientific knowledge about several neurological and psychiatric diseases will be very important for treatment decision in the near future [5].

Finally, the incorporation of biostatistics and long-term system analysis tools are at the cornerstone of the system's ability to improve quality and to adapt either to professionals, patients, institutional, or various clinical context needs or trends. This is similar to what can be achieved with some of the most advanced medication management information technology [57].

Conclusions

We are now able to start clinical trials to test and measure intensive cognitive training protocols and to evaluate its positive and also possibly negative effects on a variety of diseases and settings [52,58]. The quantification of the economic impact and health gains of these strategies for health systems is also a priority [1]. The system will continue to evolve, basically with the development of new exercises and features to accommodate the needs from diverse populations and clinical settings of operation.

Acknowledgments

This project was funded by research grants from the Portuguese Society of Neurology in 2009 and Grünenthal Foundation in 2010.

Conflicts of Interest

VTC and JP are shareholders of Neuroinova, Lda, a company that commercializes COGWEB-related products.

Multimedia Appendix 1

Web-based cognitive training system presentation for patients.

[MP4 File (MP4 Video), 3MB - resprot_v2i2e59_app1.mp4]

Multimedia Appendix 2

Exercise books presentation for patients.

[MP4 File (MP4 Video), 3MB - resprot_v2i2e59_app2.mp4]

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Abbreviations

COGWEB: Web-based cognitive training system

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Cognitive training

Article II – **Web-based cognitive training: patient adherence and intensity of treatment in an outpatient memory clinic**

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Original Paper

Web-Based Cognitive Training: Patient Adherence and Intensity of Treatment in an Outpatient Memory Clinic

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Abstract

Background: Cognitive training has been playing an increasing role in the treatment of patients with cognitive deficits. This type of intervention, namely its intensity, can be optimized by incorporating information technology-based systems.

Objective: The intent of the study was to determine the treatment intensity and patient adherence to home-based cognitive training strategies (Web-based cognitive training).

Methods: A cohort of 45 patients with neurologic and psychiatric diseases attending an outpatient memory clinic (average age 50.7 years, SD 17.0; average education 7.8 years, SD 4.9) was followed over 18 months. Participants were challenged to use a Web-based cognitive training system, "COGWEB", on a daily basis, and fulfilled at least four weeks of training supervised remotely. Additionally, 11 patients attended face-to-face sessions.

Results: The average duration of continuous cognitive training was 18.8 weeks (SD 18.9). Each patient performed on average 363.5 minutes/week (SD 136.6). At 6-month follow-up, 82.8% complied with their treatment plan. The average proportion of complete weeks was 0.75 (SD 0.22). Patients with dementia trained more intensively (444.6 minutes/week), followed by patients with static brain lesion (414.5 minutes/week; P=.01). The group that held face-to-face sessions performed more training overall (481.4 vs 366.9 minutes/week), achieving a stronger expression and statistical significance in the last week of training (652.6 versus 354.9 minutes/week, P=.027).

Conclusions: Overall, the weekly training intensity was high. Patients with dementia and static lesions performed more cognitive training. Face-to-face sessions were associated with higher intensities. The combination of classical methods with information technology systems seems to ensure greater training intensity.

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KEYWORDS

cognitive training; neurorehabilitation; Web-based training; eHealth systems; training intensity; adherence; memory clinic

Introduction

Cognitive deficits are a common expression of highly prevalent neurological and psychiatric conditions that may affect individuals of all ages and usually have a long-lasting course [1]. This group of diseases includes Alzheimer's and vascular dementias, stroke, Parkinson's disease, traumatic brain injury, multiple sclerosis, bipolar disease, schizophrenia, attention

deficit hyperactivity disorder, and all sorts of developmental delays [1-4].

Health systems in general are developing more targeted approaches to these conditions, like adult memory clinics, developmental clinics, comprehensive rehabilitation centers, and community-based approaches, directed at either the older population with neurodegenerative diseases [5] or school-age children with learning disabilities [3,6]. All these strategies aim to improve care, mainly through a combination of prompt detection of cognitive deficits in populations at risk and early reference and therapeutic interventions. In spite of the huge efforts to organize and improve care, both for patients and their caregivers, most of these conditions share some ominous characteristics. They are chronic and to date have no substantial pharmacological treatments [7,8].

In this context, cognitive training has been playing an ever-increasing role in the treatment of patients with cognitive deficits. More and more studies have reported some beneficial effects of cognitive training in ageing [9], mild to moderate Alzheimer's disease and vascular dementia [10], Parkinson's disease [11], stroke and brain injury [12], multiple sclerosis [13,14], depression, or schizophrenia [15]. In addition, some data gathered also support the idea that improvements attributed to training may generalize beyond task-specific skills [16-18], but this remains controversial due to the lack of randomized trials with appropriate controls [10,19,20]. Mostly due to methodological issues, the evidence gathered is far from providing a clear demonstration of the benefits of cognitive training and much effort is warranted to improve the design of future interventions and trials [10,21-24].

In addition, scientific discussion in the field has been raising some additional questions: (1) how to deliver this type of treatment efficiently to larger numbers of patients in need of it, (2) how to monitor and control its effects over long periods of time in real-life clinical settings, and (3) how to accommodate the increasing knowledge of neuroplastic properties of the brain and future neuro-pharmacological tools [21,25,26].

Since the number of patients that could be eligible for this type of treatment is ever increasing, it is essential to develop and validate new strategies that may improve access without elevating the costs to deliver such care [6,27]. The incorporation of computers and information technology-based systems in our current practice may optimize cognitive interventions, namely their intensity, patient adherence, and quality of professional monitoring [28-31].

We have been working on a previously described Web-based cognitive training system, "COGWEB", since 2005. Over the years, its characteristics were tailored to address major needs identified in a memory clinic setting [32-34]. This clinic organizes and delivers care to a population of 400,000, and is based in a hospital institution with clinical and research activities.

With the present study, we aimed to analyze aspects of the quality of the cognitive training delivered, specifically, adherence and continued use of the training program in the most important subgroups of diseases attending an ordinary memory clinic setting. This was a follow-up study, focused on the investigation of the intensity of cognitive training achieved and patient adherence to treatment, using COGWEB to deliver home-based cognitive training over long periods of time.

Methods

Clinical Setting and Patient Selection

The study was based in a memory clinic that provides care to neurologic and psychiatric patients of all ages (adult and pediatric) with cognitive impairment, irrespective of their baseline disease. The resident staff members include neurologists and neuropsychologists, who collaborate with other departments in a tertiary hospital. Patients are referred to this clinic by other neurologists, neurosurgeons, psychiatrists, rehabilitation medicine physicians, pediatricians, internists, or general practitioners. From this outpatient memory clinic, consecutive patients that fulfilled all of the following inclusion criteria were selected: (1) medical diagnosis of a neurologic or psychiatric condition known to produce cognitive impairment, (2) cognitive deficits confirmed by comprehensive neuropsychological evaluation using tests validated for the Portuguese population, covering domains such as attention, memory, language, executive functions, and constructional ability and selected on the basis of pathology and patient characteristics (scores were reviewed by two senior neuropsychologists and each patient was classified as having or not having a deficit in each cognitive domain), (3) at least four years of formal education completed and ability to use personal computers and information technology applications, (4) favorable opinion of the attending physician and neuropsychologist toward enrollment in cognitive training activities, (5) no sensory or physical deficiency that could prevent the independent use of personal computers and information technology applications (eg, blindness, hemiplegia, or amputation), and (6) informed consent from both the patient and relative.

There were no limits of age for inclusion. Patients were first proposed by their attending physician for enrollment in cognitive rehabilitation strategies between July and December 2011. For data analysis, only the patients that had started their treatment at least four weeks before the end of the study (18 months after study beginning) were considered. This was done to guarantee a minimum follow-up time for the within-subjects adherence analysis. During the enrollment period, 240 patients were assessed at the clinic for the first time, of which 30 were classified as not having cognitive impairment. Of those remaining, 80 did not fulfill the required level of education or ability to use personal computers. Additionally, patients were deemed ineligible due to the severity of their disease or comorbidities (n=48), sensory or physical deficiency complicating stroke, diabetes, or cataracts (n=7), and no available relative to sign the informed consent (n=3).

Due to the heterogeneity of the conditions at this memory clinic [32], and to facilitate the analysis of data, patients were grouped according to their baseline pathology into four groups: (1) neurodegenerative diseases (eg, mild stages of Alzheimer's disease, frontotemporal dementia, or Parkinson's disease), (2)

memory complaints with depressive symptoms, (3) static brain lesions (eg, stroke, traumatic brain injury, or encephalitis), and (4) other diseases (eg, epilepsy, inflammatory diseases, schizophrenia, or attention deficit hyperactive disorder).

Ethical Issues

All patients and caregivers understood the purpose of the study and provided written informed consent. Approvals from the referring neurologists were also obtained to guarantee that the expectations of patients and caregivers were properly managed. This study was approved by the hospital review board and ethics commission (Hospital São Sebastião, Centro Hospitalar de Entre o Douro e Vouga, Santa Maria da Feira, Portugal).

Cognitive Intervention

Main Characteristics of COGWEB

The COGWEB system allows for the implementation of personalized cognitive training programs remotely, in the patient's living environment, under continuous supervision by experienced neuropsychologists [32]. The version used for this study was composed of 27 independent exercises in a computerized game format, developed to train various degrees of cognitive defects from mild to more severe impairments. Each exercise is organized primarily around a specific cognitive function, such as attention, executive functions, memory, language, praxis, gnosis, and calculus. Exercise progression is automatic through several levels of difficulty that change in accordance with the patient's performance and are coupled with support messages in real-time. The different degrees of difficulty are obtained through the manipulation of some features such as the number and type of items per level, their intrinsic complexity, or the interval between stimuli. All exercises use random, non-sequential stimuli to prevent memorization and maintain motivation between sessions. There are also several progress graphs (eg, right answers vs wrong answers, levels completed, global training time, or accesses) that are used to motivate patients after revision by the professional in charge [32,34].

Cognitive Training Design and Methods Used

The activities concerning cognitive training plans were all supervised by the resident neuropsychologist, who also conducted comprehensive neuropsychological assessments according to the patient medical diagnosis and using tests validated for the Portuguese population. All patients performed Web-based cognitive training, using the COGWEB system [32,34]. The training sessions were performed outside the hospital, predominantly at patients' homes or other comfortable family or social settings. The neuropsychologist tailored the cognitive training plan to the patients' medical conditions and cognitive deficits, thus contents of the training sessions varied during the course of the rehabilitation program. Sessions could include exposure to different combinations and proportions of exercises focused either on memory, executive functioning, attention, language, calculation, or constructive ability. The personalization of the cognitive training plans included the following possibilities (COGWEB system features): (1) recommended duration of each daily session, (2) number of sessions per week, (3) time of the day where most training should take place (morning or afternoon), (4) type, number, initial level of difficulty, and duration of each exercise (from a pool of 27) that composed the sessions, (5) frequency of adjustments to the exercises prescribed, and (6) frequency of progress reports from the neuropsychologist to the patient/caregiver. Patients were instructed to complete a minimum number of sessions per week (7 sessions, minimum of 30 minutes each). These could be performed at the patient and caregiver's convenience, at any time of the day in consecutive days or up to 4 sessions per day. Anything below this limit was considered non-adherence. There were no restrictions or indications of a maximum time of treatment per week.

Based on the clinical judgment of the neuropsychologists and attending physicians, some patients had their training programs based primarily on weekly face-to-face sessions with a neuropsychologist, either individualized or group sessions with an average duration of 60 minutes. Their internal organizations were defined by the neuropsychologists, according to each patient's baseline assessment and ongoing Web-based cognitive training activities. In the specific setting of the memory clinic where the study was based, face-to-face sessions are used primarily in the rehabilitation programs of younger patients with not only static brain lesions, which are usually more severe, but also with a higher potential for socioprofessional reintegration. Older patients with stroke and early dementia may also receive this type of treatment but mainly in group sessions.

Study Flow

In total, 72 patients fulfilled the inclusion criteria during the recruitment period. From these, 63 patients met all conditions that allowed them to start using the COGWEB system as part of their training program. Nonetheless, 8 patients (12.7%) did not actually start and 10 (15.6%) had used the system for a period of less than four weeks at the time of the analysis (Figure 1).

The analysis was conducted on a final sample of 45 patients with a mean age of 50.7 years (SD 17.0, range 11.0-84.0), mean years of formal education of 7.8 (SD 4.9, range 4.0-17.0), and 16 (35.6%) were female. According to their baseline pathology, of the 45 patients, 9 (20.0%) had definite neurodegenerative diseases, 14 (31.1%) had memory complaints with depressive symptoms, 15 (33.3%) had static brain lesions, and 7 (15.6%) had other diseases (Table 1). Patients that interrupted their treatment plan due to technical problems with the Internet at home or by their own decision were considered as non-adherent with treatment plan (Figure 1).

The 18 patients excluded from the analysis after agreeing to use COGWEB had a mean age of 49.0 (SD 17.4, range 19.0-78.0), mean years of formal education of 10.6 (SD 4.6, range 4.0-17.0), and 42% were female. Their baseline pathologies were: 22.2% (4/18) neurodegenerative diseases, 22.2% (4/18) memory complaints with depressive symptoms, 38.9% (7/18) static brain lesions, and 16.7% (3/18) other diseases.

Figure 1. Study flowchart.

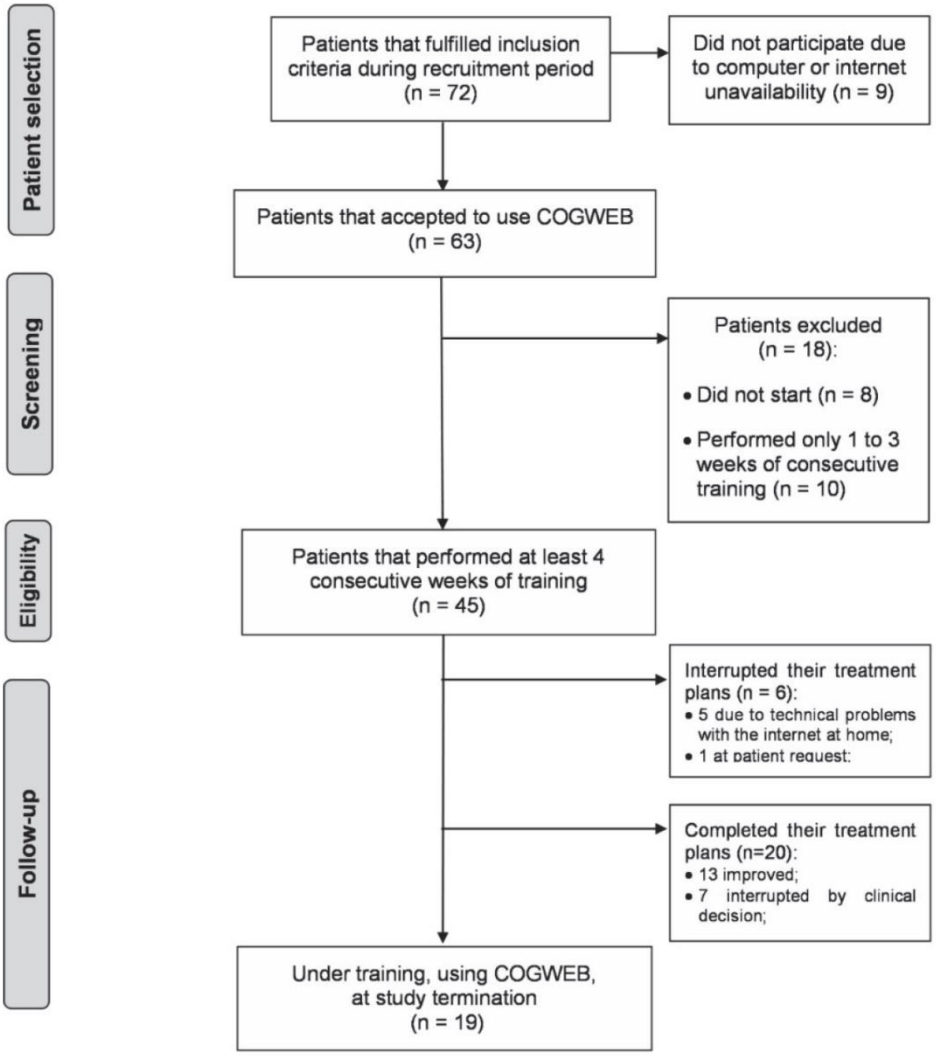


Table 1. Demographic characteristics of all groups.

Characteristics		Neuro-degenerative diseases, (n=9)	Memory complaints/ depression, (n=14)	Static brain lesions, (n=15)	Other diseases, (n=7)
Age (years), mean (SD)		61.8 (5.7)	54.8 (13.8)	44.2 (19.5)	44.6 (19.5)
Gender, n (%) male		8 (88.9)	6 (42.8)	11 (73.3)	4 (57.1)
Formal education (years), mean (SD)		6.5 (4.6)	6.1 (4.1)	9.2 (4.3)	9.9 (6.7)
Baseline cognitive performance, n (%) with deficit					
	Attention	9 (100.0)	12 (85.7)	13 (86.7)	4 (57.1)
	Memory	8 (88.9)	7 (50.0)	14 (93.3)	9 (100.0)
	Language	4 (44.4)	0 (0.0)	3 (20.0)	1 (14.3)
	Executive functioning	9 (100.0)	3 (21.4)	12 (80.0)	5 (71.4)
	Constructional ability	4 (44.4)	0 (0.0)	2 (13.3)	1 (14.3)
Face-to-face sessions, n (%) exposed		3 (33.3)	0 (0.0)	7 (46.7)	1 (14.3)

Outcome Definition

The COGWEB system allowed for the continuous monitoring of the following outcomes: (1) expected time of training (minutes)—summation of the duration of all prescribed sessions of training during the follow-up period of each patient, (2) time spent training (minutes)—summation of the duration of all sessions actually performed by the patient, (3) cumulative time of training in the first and last week of follow-up (minutes/week)—time of training in the first and last weeks, (4) assiduity—difference between the minimum number of sessions prescribed and the number of sessions actually performed, expressed as the proportion of complete weeks, and (5) follow-up period (weeks)—duration of consecutive time in training for each patient, with interruptions of more than one week duration being considered as study termination and the end of the follow-up period for a particular patient. This was further categorized as withdrawal due to non-adherence or termination according to treatment plan. The first two outcomes were used to measure the intensity of cognitive training obtained and the last three to measure motivation and adherence to treatment. Cognitive training plans were also classified as exclusively Web-based if all treatment activities occurred through the COGWEB, or combined when there was weekly face-to-face cognitive training work complemented with Web-based cognitive training activities.

Statistical Analysis

The SPSS Statistics version 21.0.0 software was used [35]. In order to characterize the global sample, mean values and standard deviations were used to describe outcomes, and parametric tests for statistical analysis were: ANOVA (analysis of variance), Student's *t* test for independent groups, and paired *t* test for within-subject comparison of cumulative time of training in the first and last week. For subgroup description, the median and interquartile ranges (IQR) were used as they are more suitable to the size and type of distribution within each group sample. To analyze the differences in outcomes between subgroups, the Kruskal-Wallis independent samples median test was used, adjusting for multiple comparisons. The related samples Wilcoxon signed-rank test was used to compare the first and the last weeks of training within each subgroup. The independent samples Mann-Whitney *U* test was used to compare the main demographic characteristics and the outcome differences between the group with exclusive Web-based training and the group with face-to-face sessions complemented with Web-based training. Fisher's exact test and chi-square were used to compare baseline characteristics such as gender, distribution of groups of diseases, and cognitive domains impaired, between subgroups. The effect of face-to-face sessions within subgroups of diseases was not analyzed due to the reduced sample size. Finally, an analysis of the probability to comply with the Web-based cognitive training was conducted using the Kaplan-Meier survival method in order to model the duration time of the treatment up to its interruption. Patients completing the treatment plan or undergoing training at the time of the follow-up were censored.

Results

Intensity of Treatment Obtained

For the duration of the entire follow-up period, patients performed on average 363.5 minutes/week (SD 136.6, range 84.7-652.6) of cognitive training activities through the COGWEB system. This was 1.7 times higher than the minimum requirement.

The analysis of the mean time training per week between groups of diseases revealed significant differences (Figure 2 and Table 2), with neurodegenerative diseases and static brain lesions dedicating more time to training (H_3=11.41, P=.01). There was no association of mean time training per week with potential confounders like age ($F_{1,41}$=0.86, P=.36), gender (t_{42}=−1.64, P=.11) or education ($F_{1,41}$= 0.70, P=.41).

Figure 2. Time spent training (average in minutes/week) per disease group.

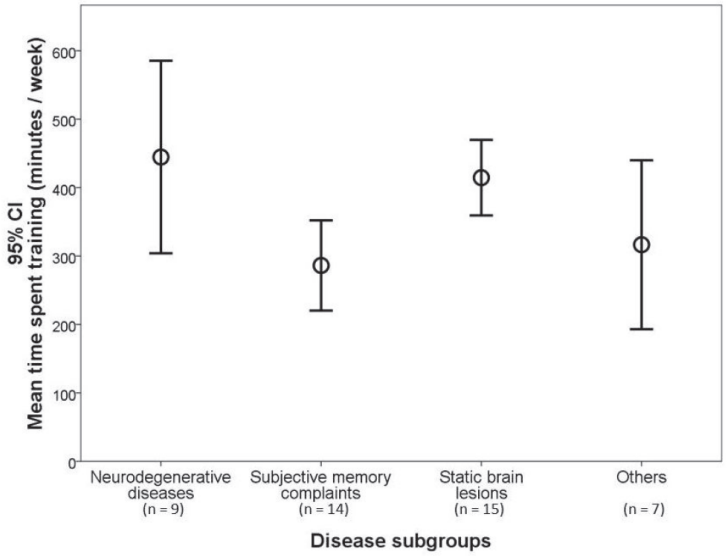


Table 2. Indicators of intensity and adherence to treatment per major group of diseases.

	Neurodegenerative diseases, median (interquartile range)	Memory complaints/ depression, median (interquartile range)	Static brain lesions, median (interquartile range)	Other diseases, median (interquartile range)
Follow-up duration (weeks)	26 (7.8-29.8)	22.5 (7.8-33.5)	8 (5.0-25.0)	11 (7.0-18.0)
Time training per week (minutes)	479.0 (257.6-567.7)	295.3 (187.3-404.0)	423.6 (362-458)	295.6 (203.7-366.9)
Time training, first week (minutes)	555.9 (159.0-806.0)	308.3 (143.2-579.8)	501.9 (442.9-656.3)	173.3 (99.7-491.8)
Time training, last week (minutes)	394.6 (201.0-639.4)	282.5 (73.3-576.2)	376.0 (279.8-804.8)	379.5 (254.3-443.2)
Assiduity (proportion of complete weeks)	0.89 (0.53-0.96)	0.73 (0.55-0.84)	0.80 (0.75-1.0)	0.63 (0.53-0.83)

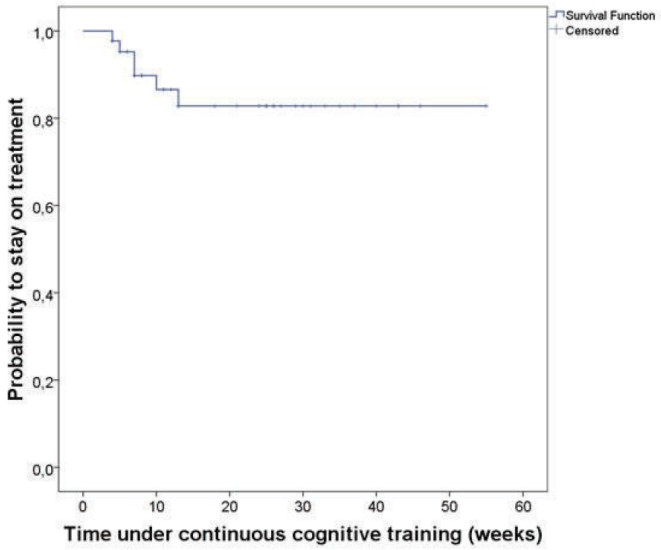
Adherence to Treatment

The average duration of continuous cognitive training was 18.8 weeks (SD 18.9, range 4.0-55.0), and there were no statistically significant differences among groups (H_3=3.40, P=.33) (Table 2). During the first week, the average time training was 428.7 minutes (SD 264.8, range 21.0-891.0). In the final week, this value was 414.5 minutes (SD 268.1, range 21.1-969.0). These values were not statistically different (t_{43}=0.27, P=.79). There were no differences of mean time training between first and last week attributable to any of the major group of diseases (Z=22.00, P=.58 for neurodegenerative diseases; Z=53.00, P=.98 for memory complaints with depression; Z=63.00, P=.87 for static brain lesions; Z=14.00, P=1.00 for other diseases) (Table 2).

The average proportion of complete weeks of training (measure of assiduity) was 0.75 (SD 0.22, range 0.18-1.0) and there were no difference between groups (H_3=4.04, P=.26) (Table 2).

The application of the Kaplan-Meier method estimated an average duration of continuous Web-based cognitive treatment of 46.9 weeks (SD 3.03), with 95% confidence intervals of 41.3 and 52.8 weeks. At 6-month follow-up (24 weeks), 82.8% of patients complied with their treatment plan (Figure 3).

Figure 3. Probability of continuing with treatment over time (Kaplan-Meier survival function) for the first 60 weeks. There were no treatment interruptions after this period. Patients completing the treatment plan or undergoing training at time of follow-up were censored.



Impact of Face-to-Face Sessions

During the follow-up period, 11/45 patients (24.4%) received weekly face-to-face sessions complemented with Web-based training (63.6%, 7/11 static brain lesions, 27.3%, 3/11 neurodegenerative, and 9.1%, 1/11 other diseases). Patients with memory complaints and depressive symptoms were excluded from this analysis since none in this subgroup was exposed to face-to-face sessions (Table 1). The baseline characteristics of the two groups are depicted in Table 3. There were no significant differences regarding age (U_{28}=123.0, P=.425), formal education (U_{28}=286.5, P=.718), gender (χ^2_1=0.6, P=.42), and distribution of the groups of diseases (χ^2_2=1.8,

P=.42) between the two groups. The distribution of cognitive impairment by domain was also similar (Table 3).

Table 3. Demographic characteristics of the groups used for analysis of the impact of face-to-face sessions.

Characteristics		Exclusively Web-based training (n=20)	Face-to-face sessions complemented with Web-based training (n=11)
Age (years), mean (SD)		50.0 (19.9)	47.2 (15.6)
Gender, n (%) male		13 (65.0)	9 (81.8)
Formal education (years), mean (SD)		8.5 (5.2)	8.9 (5.1)
Major groups of diseases, n (%)			
	ND[a]	6 (30.0)	3 (27.3)
	SBL[b]	8 (40.0)	7 (63.6)
	OD[c]	6 (30.0)	1 (9.1)
Baseline cognitive performance, n (%) with deficit			
	Attention	17 (85.0)	9 (81.8)
	Memory	18 (90.0)	11 (100.0)
	Language	5 (25.0)	3 (27.3)
	Executive functioning	16 (80.0)	10 (90.9)
	Constructional ability	4 (20.0)	3 (27.3)

[a]ND: neurodegenerative diseases

[b]SBL: static brain lesions

[c]OD: other diseases

The median duration of the follow-up was higher in the group with face-to-face sessions: 26.0 weeks (IQR=7.0–43.0; min. 4.0, max. 55.0) vs 11.0 weeks (IQR=6.0–18.0; min. 4.0, max. 40.0) in the group with exclusively Web-based training. However, there was no statistical significance (U_{28}=70.5, *P*=.145) (Table 4). The overall median time training per week in the group with face-to-face sessions was 481.4 minutes (IQR=398.4–577.3; min. 180.4, max. 652.6), while in the group with exclusively Web-based sessions it was 366.9 minutes (IQR=281.3–452.5; min. 191.3, max. 583.0). This difference had no statistical significance (U_{28}=62.0, *P*=.07). In the last week of the cognitive intervention, significant differences were verified in the median time training between the two groups with 652.6 minutes (IQR=379.5–817.4; min. 279.8, max. 969.0) when there were face-to-face sessions vs 354.9 minutes (IQR=138.5–577.3; min. 21.1, max. 857.0) when exclusively Web-based (U_{28}= 53.0, *P*=.027). These differences were not present in the first week of training (U_{28}=106.0, *P*=.949) (Table 4). The overall assiduity was not different between these two groups during the study (U_{28}=82.0, *P*=.33).

Table 4. Indicators of intensity and adherence to treatment per major type of treatment strategy.

	Exclusively Web-based training (n=20), median (interquartile range)	Face-to-face sessions complemented with Web-based training (n=11), median (interquartile range)
Follow-up duration (weeks)	11.0 (6.0-18.0)	26.0 (7.0-43.0)
Time training per week (minutes)	366.9 (281.3-452.5)	481.4 (398.4-577.3)
Time training, first week (minutes)	489.3 (145.9-662.9)	490.7 (173.3-655.2)
Time training, last week (minutes)	354.9 (138.5-577.3)	652.6 (379.5-817.4)
Assiduity (proportion of complete weeks)	0.75 (0.3-1.0)	0.83 (0.4-1.0)

Discussion

Principal Findings

This study provided data on the characteristics of cognitive training treatments using a Web-based approach in an ordinary memory clinic setting. The overall intensities of training obtained were very high, averaging 6 hours per week and exceeding 1.7 times of what was set as minimum. Furthermore, the characteristics of the system used (COGWEB) permitted uninterrupted training activities over long periods of time, with 82.8% of patients complying with treatment at 6 months. The combination of high intensity and long duration of treatment is very important to stimulate neuroplasticity in the brain [21], more so, if we consider the design of future randomized clinical

trials to assess the impact of cognitive training on functional outcomes in several important diseases [21,23,36].

Significant differences were found in the mean intensity of treatment obtained between groups, with neurodegenerative diseases and static brain injury performing around 7 hours of training per week, while people with memory complaints and depressive symptoms trained close to 5 hours per week. It is important to point out that all groups performed above the minimum requirements of 30 minutes of training per day (same for all). Engaging psychiatric or neurologic patients in training or interesting leisure activities is very difficult [37]. As an example of the current state of the art, even in inpatient mental health services of developed countries, the level of activities, other than sleep, eating, or watching TV, is less than 17 minutes per day [37]. This is in high contrast with what was obtained in this study for the several groups of diseases analyzed.

During the follow-up period of the 45 patients included, and specifically comparing the first and the last week of training, the intensity of treatment did not decay and there were no important effects attributable to the major disease groups. Furthermore, follow-up duration between major groups of diseases did not differ. Although neurodegenerative disease patients had a tendency to have longer follow-up periods (around 7 months), this could be explained only by clinical reasons, with static brain lesions being prescribed shorter periods of training. These latter findings may be due to the reduced sample size for subgroup analysis.

An interesting finding of this study was the effect of weekly face-to-face sessions on the overall intensities of Web-based cognitive training activities. The group exposed to face-to-face sessions performed, on average, 2 additional hours of training per week during the entire duration of the follow-up period. This difference was not present in the first week of training, but was built over time and achieved a value of 4 hours and statistical significance in the last week of training. There was a trend for longer follow-up periods in the group with face-to-face sessions, but not achieving statistical significance. These findings are in accordance with some critical analysis of the impact of computerized cognitive training activities and the need to prevent excessive isolation of patients during treatment [38-42]. In future studies, if the intensity of treatment and adherence are to be maximized, the inclusion of some kind of periodic face-to-face individual or group session is warranted. Nonetheless, to clarify the impact of different methods of face-to-face sessions (eg, individual, group, weekly, monthly) and whether they are reproducible between groups of diseases, further studies are necessary.

Limitations

The limitations of this study are mainly inherent to the uncontrolled nature and single center design, which impose some restrictions on the generalizability of the findings. In this respect, it is important to note that from the 240 patients initially assessed, 80 (33.3%) did not fulfil the required levels of literacy or ability to use personal computers and information technology applications. Furthermore, among the patients that fulfilled inclusion criteria, 9 out of 72 did not participate due to personal computer or Internet unavailability and 8 out of 63 did not start after agreeing to participate. These values may reflect the low literacy levels and barriers in patient access to information technology at home, in this segment of the Portuguese population [43]. Although the trends are changing [44], these aspects are still significant in the population aged over 50 and must be taken into consideration in the implementation of this type of cognitive intervention in clinical practice or future research.

In addition, the focus of this work was on obtaining data on the intensity and adherence to treatment and for that reason blinded information on cognitive baseline or outcome measures was not collected. The patient's diagnosis only conveys indirect information on patient deficits and level of impairment, with baseline cognitive performance data provided only partially addressing this limitation. Despite the inclusion criteria defined, the enrollment of patients in the study was based upon a referral by their attending physician and neuropsychologist's judgment. They decided whether the patient would comply with treatment and also if the deficits and background literacy or cognitive reserve were suitable. Face-to-face sessions were also decided on clinical indication and not randomized. The role of the professionals in patient selection in both these situations may have biased the results in a direction consistent with the findings. Furthermore, differences between first and last week intensities may also be due to selection biases attributable to the professional intervention. The heterogeneity of diagnoses was also a potential weakness and should not be maintained in trials evaluating clinical efficacy.

Future studies must analyze the impact of up to 7 hours of cognitive training per week on global motor activities, sedentarism indexes [45], and also possible negative mental effects of uncontrolled cognitive training activities [46]. These latter aspects are similar to the risks associated with unsupervised "of-the-shelf" home rehabilitation activities and learned non-use models during aphasia or motor rehabilitation after stroke [47-49]. They may only be avoided through control of several aspects of training like activities preformed, cumulative dose of training in each cognitive domain, and specific cognitive outcomes along time.

Conclusions

Overall, the training intensity achieved per week was high. The groups of patients with dementia and static lesions performed more cognitive training. Patients with additional face-to-face sessions achieved a higher intensity workout. The combination of classical methods with information technology-based systems like COGWEB seems to be the option that ensures greater training intensity. This method should be further explored in multicenter randomized controlled trials targeted at the most prevalent diseases like dementia, stroke, schizophrenia, or multiple sclerosis.

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Authors' Contributions

Cruz, Pais, and Coutinho obtained funding and were responsible for study concept and design. Cruz, Pais, Alves, Mateus, Ruano, Barreto, Bento, and Colunas were responsible for acquisition of data. Analysis and interpretation of data was performed by Cruz, Pais, Ruano, Rocha, and Coutinho. All authors participated in critical revision of the manuscript for important intellectual content. Administrative, technical, and material support was provided by Alves, Ruano, Mateus, Barreto, Bento, and Colunas, and study supervision was performed by Cruz, Pais, Bento, Colunas, Rocha, and Coutinho.

Conflicts of Interest

Cruz and Pais have a shareholder position at Neuroinova, Lda, a company that develops and commercializes COGWEB-related products. Bento and Colunas received fees for the technological development of COGWEB. Alves, Ruano, Mateus, Barreto, Rocha, and Coutinho have no conflicts of interest to report.

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Abbreviations

ANOVA: analysis of variance
COGWEB: cognitive Web-based training system
IQR: interquartile range

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Cognitive training

Article III – **Implementation and outcomes of a collaborative multi-center network aimed at web-based cognitive training – COGWEB network**

Cruz VT, Pais J, Ruano L, Mateus C, Colunas M, Alves I, Barreto R, Conde E, Sousa A, Araújo I, Bento V, Coutinho P, Rocha NP, COGWEB network collaborators

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Original Paper

Implementation and Outcomes of a Collaborative Multi-Center Network Aimed at Web-Based Cognitive Training – COGWEB Network

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Abstract

Background: Cognitive care for the most prevalent neurologic and psychiatric conditions will only improve through the implementation of new sustainable approaches. Innovative cognitive training methodologies and collaborative professional networks are necessary evolutions in the mental health sector.

Objective: The objective of the study was to describe the implementation process and early outcomes of a nationwide multi-organizational network supported on a Web-based cognitive training system (COGWEB).

Methods: The setting for network implementation was the Portuguese mental health system and the hospital-, academic-, community-based institutions and professionals providing cognitive training. The network started in August 2012, with 16 centers, and was monitored until September 2013 (inclusions were open). After onsite training, all were allowed to use COGWEB in their clinical or research activities. For supervision and maintenance were implemented newsletters, questionnaires, visits and webinars. The following outcomes were prospectively measured: (1) number, (2) type, (3) time to start, and (4) activity state of centers; age, gender, level of education, and medical diagnosis of patients enrolled.

Results: The network included 68 professionals from 41 centers, (33/41) 80% clinical, (8/41) 19% nonclinical. A total of 298 patients received cognitive training; 45.3% (n=135) female, mean age 54.4 years (SD 18.7), mean educational level 9.8 years (SD 4.8). The number enrolled each month increased significantly (r=0.6; P=.031). At 12 months, 205 remained on treatment. The major causes of cognitive impairment were: (1) neurodegenerative (115/298, 38.6%), (2) structural brain lesions (63/298, 21.1%), (3) autoimmune (40/298, 13.4%), (4) schizophrenia (30/298, 10.1%), and (5) others (50/298, 16.8%). The comparison of the patient profiles, promoter versus all other clinical centers, showed significant increases in the diversity of causes and spectrums of ages and education.

Conclusions: Over its first year, there was a major increase in the number of new centers and professionals, as well as of the clinical diversity of patients treated. The consolidation of such a national collaborative network represents an innovative step in

mental health care evolution. Furthermore, it may contribute to translational processes in the field of cognitive training and reduce disease burden.

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KEYWORDS

cognitive training; neurorehabilitation; eHealth systems; memory clinic; collaborative network; stroke; dementia; schizophrenia; mental health services

Introduction

Professional Collaborative Networks and Cognition Care

The evolution of health systems is increasingly dependent on professional collaborative networks [1,2]. This type of solution has been thoroughly explored in social, governmental, commercial, and enterprise competitive settings [3,4]. Nonetheless, in the health care setting, there is a limited understanding of the network dynamics, internal processes, key structural features, or how to evaluate their outcomes [5-7].

In general, professionals see collaboration as necessary, and their main expectations are to establish interprofessional relations that would lead to greater efficiency, better knowledge of other institutions, and professional support [8]. However, most health care settings are prone to generate isolated clusters, like professional groups, medical specialties, organization departments, and units [9]. They usually are kept apart due to physical, cultural, cognitive, or trust barriers [10].

The mental health sector, mainly due to demographic and economic constraints on health resources, is under increasing pressure to self-reshape and implement new sustainable approaches [11-13]. This situation has been enlightening groups and key players, at several hierarchic levels of decision, to the advantages of working together in search of synergies and more effective ways to deliver mental care [2,11,14].

Cognitive deficits associated with the most prevalent neurologic and psychiatric diseases represent 11.2% of the global burden of disease worldwide, accounting each year for 30 new cases per 1000 inhabitants [15]. Nowadays, treatment of cognitive deficits largely relies on specialized human mediated interventions (eg, cognitive rehabilitation, training, stimulation, or remediation), with pharmacological options far from playing an important role [16]. The combination of these factors renders most mental health systems worldwide largely unable to meet cognitive rehabilitation needs, either in due time after injury or adequate intensities [2]. To adequately meet these new demand patterns without increasing health care costs, sustainable organizational changes are necessary [2,17]. In addition, the clinical use of information technology based systems is known to improve cognitive interventions, namely their intensity, patient adherence, and quality of professional monitoring [18-21].

An Innovative Web-Based Cognitive Training System

With this global scenery in mind, starting in 2005 in a memory clinic setting, we developed an innovative Web-based cognitive training system, named COGWEB and described elsewhere [22-24]. Over time, the system evolved to address the needs of patients, professionals, and organizations in the field of cognitive rehabilitation [22,25]. It was designed to: (1) improve the efficiency of home-based cognitive training procedures; (2) increase patient access to care; (3) shift the therapeutic footprint from hospital to patient comfort zones; and most importantly, (4) to foster collaborative work between professionals from geographically distributed centers [24,25]. This set of characteristics made the COGWEB system especially suited to be the promoter of a new collaborative network, sharing specialized knowledge, improved procedures, innovative tools, and connecting professionals and institutions dedicated to cognitive rehabilitation.

The aim of this paper is to describe the implementation, early outcomes, and sustainability, over its first year of functioning, of a nationwide multi-organizational cognitive interventional network, taking advantage of the characteristics of an innovative Web-based cognitive training system.

Methods

National Setting

Cognitive Interventions

The Portuguese mental health sector has some specificities [26], nevertheless most of its organization is comparable to Western European models of care [15,27]. Neuropsychological rehabilitation is performed in different and almost unrelated settings in Portugal [28]. If we consider all forms of cognitive intervention provided (rehabilitation, training, stimulation, or remediation) along mental health services, as defined by the World Health Organization [15,27] and the National mental health plan [26,29], we may group them in the following ways.

Referral Institutions With Medical Supervision or Integrated in Multi-disciplinary Clinical Departments

The adult outpatient memory clinics in neurology and psychiatry departments are mainly dedicated to neuropsychological assessment, but some of them are also interested in providing rehabilitation care.

The day centers within psychiatric clinics and departments are dedicated to patients with schizophrenia, major depression, or bipolar disorder. Some of them provide social and cognitive remediation programs.

The referral rehabilitation hospitals are chiefly dedicated to traumatic brain injury patients and young patients with anoxic damage, stroke, multiple sclerosis, encephalitis, and postneurosurgery.

The outpatient rehabilitation clinics are largely run by rehabilitation medicine specialists and dedicated to motor rehabilitation of neurologic diseases, but they are developing a growing interest for cognitive rehabilitation.

The developmental clinics in pediatric departments are primarily concerned with early detection of motor and mental delays, and psychosocial interventions, a few of them having specialized human resources dedicated to cognitive rehabilitation.

Community Services, Supervised by Allied Health Professionals Including Psychologists, Occupational Therapists, Social Workers, or Rehabilitation Nurses

The community day centers and residential facilities dedicated to neurodegenerative diseases and providing cognitive care are mainly focused in cognitive stimulation and training of activities of daily living.

The community day centers and residential services are dedicated to children and adults with cerebral palsy and other inborn causes of intellectual disability.

Community Services Related With the Educational System, Not Included in the Health System

There are psychology and special education services at schools of the National Ministry of Education. There are also study centers dedicated to the compensation of learning difficulties. Additionally, there are adult and senior learning services.

Academic Centers Dedicated to Basic and Clinical Neurosciences

These centers are generally in partnership with institutions from the above categories.

Patient Care Limitations

In spite of the variety of services, patient access to care is limited by several important factors: (1) the location of patients' home (urban vs suburban or rural), (2) socioeconomic status, (3) mobility, and (4) the level of education of patients and families [26,27]. Furthermore, National Health Service standards of care do not include global access to cognitive interventions [29]. This leads to great heterogeneity on the level of service available, and the type of providers (private vs governmental) between regions [28]. The standards of professional care and practices, certification and training, and how those standards are maintained over time are also not perfectly established [27,28]. Outside of hospitals or other medical institutions, the clinical responsibility for cognitive interventions or local multi-disciplinary teams' coordination is difficult to understand solely based on professional certification and specialized training [26,28,29].

Promoter Center Setting

The clinical center where the initial research and development of COGWEB took place was an outpatient memory clinic. This was based in a neurology department in a tertiary hospital that provided care to 400,000 inhabitants. The resident clinical staff included neurologists and neuropsychologists. Patients with suspected cognitive deficits, irrespective of their cause, were referred to this clinic for diagnosis and rehabilitation by other neurologists, neurosurgeons, psychiatrists, rehabilitation medicine physicians, pediatricians, internists, or general practitioners [23].

Development and Main Functionalities of COGWEB

The COGWEB system is a Web-based working tool that allows for the implementation of personalized cognitive training programs remotely, in the hospital, or patient's living environment, under continuous supervision by experienced neuropsychologists [24]. Its development started in 2005, and the first clinical center initiated its use in 2007 (promoter center). Then, the system underwent a five-year period of further technological development, refinement, and thorough clinical testing [24]. Over the last three years, this Web-based cognitive training system was integrated into regular clinical practice at the promoter center. This option led to a threefold increase in patient access to supervised cognitive training and, on average, a sevenfold increase in rehabilitation training time, while maintaining human resources expenditures [23]. More recently, a cohort study provided data on patient adherence and intensity of training obtained using this instrument over long periods of time in a common outpatient memory clinic setting [25]. The version used for this study was composed of 30 independent exercises in a computerized game format. They were developed to train various degrees of impairments in specific cognitive domains, such as attention, executive functions, memory, language, praxis, gnosis, and calculus [23,24]. The training sessions were individually prescribed on the Internet by a therapist, just after thorough cognitive assessment and according to personalized plans discussed face-to-face with each patient, as previously described [25]. Internet activities performed by the patients were summarized in several progress graphs (eg, right answers vs wrong answers, levels completed, global training time, or accesses) that were revised weekly by the professional in charge. This information was used to monitor patient's evolution, as well as to elaborate progress reports or to aid motivation [23,24].

Network Implementation Procedures

In March 2012, the most important clinical actors and institutions in the field of cognitive impairment assessment, diagnosis, and treatment in Portugal were invited to join the COGWEB network. The institutions included psychiatry, neurology, and rehabilitation medicine departments, as well as more specialized units within these structures like memory and dementia clinics, schizophrenia clinics, day hospitals, and residential facilities. At the time two national workshop meetings were organized to present the COGWEB system and the results of the first clinical studies. Additionally, actors were invited to talk about their clinical settings and difficulties to implement cognitive intervention programs in everyday practice. During the meetings all were allowed to experiment with the COGWEB system, and were formally invited to participate in a collaborative network, due to start in the near future, and with the main purposes of: (1) democratize patient access to specialized Web-based cognitive stimulation, training, or rehabilitation services; (2) putting Web-based cognitive intervention knowledge into routine practice; (3) further develop and tailor the COGWEB system to the needs and requirements

of all professionals that use it in their clinical settings, and patients in their communities; (4) foster multi-center research studies in the field of cognitive rehabilitation; and (5) create the environment necessary to foster translational pathways in the field of cognitive neuroscience. The centers that initially accepted to participate in the network were considered as the baseline group. As the network operated as an open system, all centers that joined thereafter were considered new centers for the analysis.

Network Maintenance Procedures

All centers that decided to adopt the COGWEB system were visited in person by the network founders (VTC and JP), and received the COGWEB training manuals and in-house formation on how to use the system [23,30]. The first visit had an average duration of 2 hours, and included a session with all the clinical staff enrolled in activities with patients having cognitive deficits (eg, physicians, psychologists, therapists, and nurses). This was followed by a practical workshop with the local responsible neuropsychologist and other team staff such as therapists. During this visit, a second encounter was scheduled to discuss the treatment plans of the first patients to enroll in Web-based cognitive training activities.

The final decision to include patients was the responsibility of the local professionals that selected who could benefit the most from the Web-based cognitive training. There were no restrictions related with medical diagnosis or severity of deficits.

Between visits, all centers were regularly updated on new functionalities of the system (eg, an automatic report tool, performance and assiduity alerts, tutorial videos, and Internet manual), availability of new cognitive training exercises (number went from 17 to 34 during the first year of functioning), the results of quality assessment questionnaires to patients and caregivers, and the results of research study protocols and scientific presentations at national and international meetings. This information was passed in newsletter format by email to the local responsible, and also in part diffused in the blog at the project Web page [22], and at the Facebook page. To incorporate professionals' points-of-view toward the COGWEB system, these actors were challenged to fill opinion Web-questionnaires using Google Docs. The founders' efforts to improve quality of use of the system by the professionals in active centers included regular in person visits or webinars using Skype and Google Hangouts to discuss patients and methods, with the centers that were comfortable with this type of communication. Web presentations were also used (eg, good practice advice on how to program daily sessions, information on how to use COGWEB materials in exercise book format, and clinical vignettes).

Ethical Issues

All professionals signed a specific written informed consent. All patients and caregivers also provided written informed consent. This study was approved by the hospital review board and local ethics commission at Hospital São Sebastião, Centro Hospitalar de Entre o Douro e Vouga, Santa Maria da Feira, Portugal (chair, Rui Carrapato, MD, PhD) and Portuguese National Data Protection Commission.

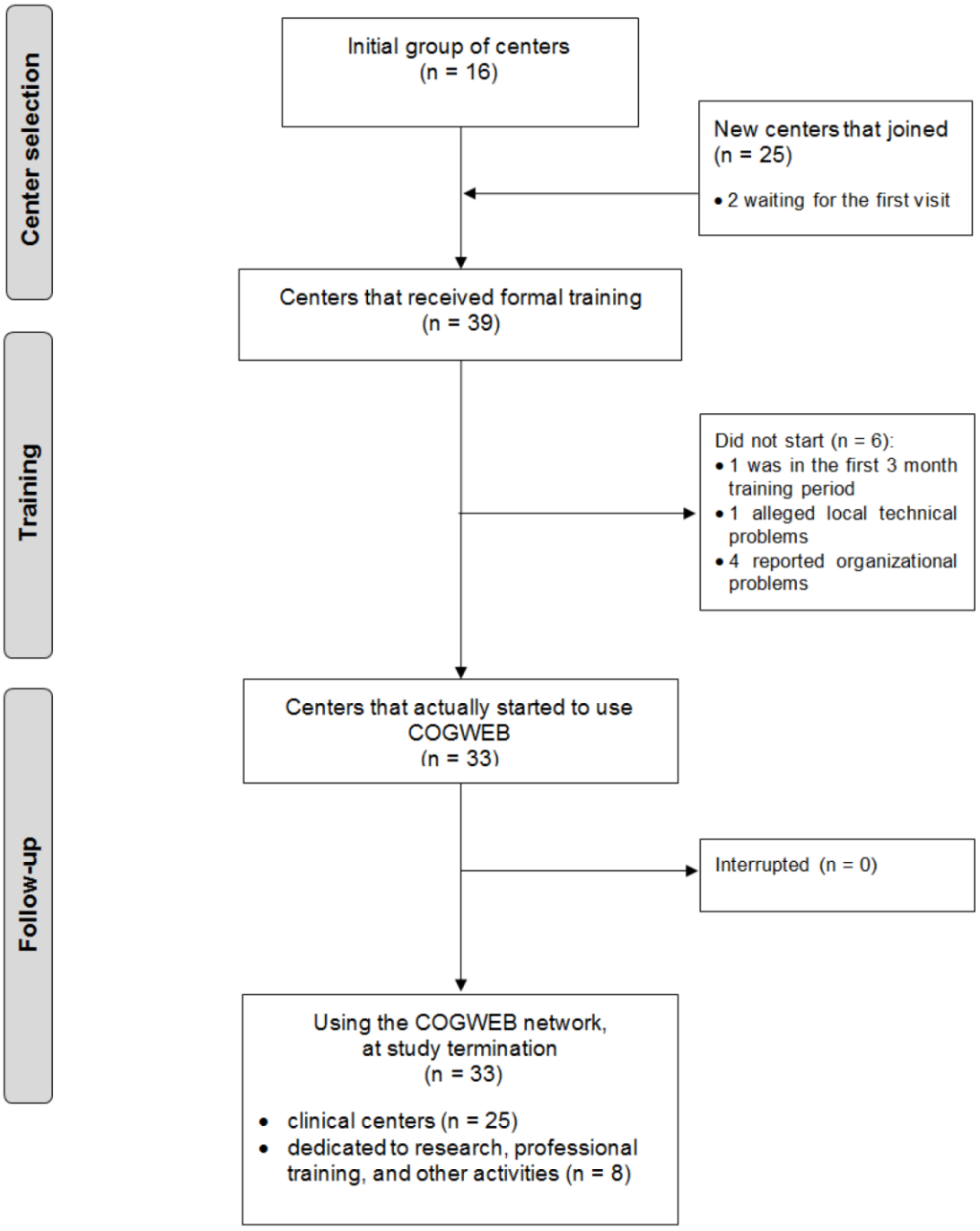
Financial Issues

Each center that was enrolled in the COGWEB network paid an annual fee to cover training costs, materials, and development of the system. These fees were supported by the centers themselves, research funding, or by third party sponsors listed in the Conflicts of Interest section. The average cost of using the system amounted to US $8.05 per patient and per month (taxes included). Human resources to manage the system locally were the responsibility of the centers.

Study Flow

There were 68 professionals from 41 centers that received formal training on the COGWEB system during the first year of functioning of the COGWEB network (Figure 1 shows this). The network behavior of these centers was analyzed between August 2012 and September 2013, according to the variables defined for the study.

Figure 1. Study flowchart.



Outcomes Definition and Analysis

To evaluate the network as a whole, the centers included were classified as clinical centers, if they were primarily dedicated to clinical activities, or nonclinical centers, if they were focused in research, professional training, and other activities. Additionally, all centers were classified according to the overall services they provided and positioning on the national mental health system setting (Table 1). The number and type of new centers and professionals that joined during the first year of implementation were the elements used to assess the network growth and degree of diversity.

For the subset of the network primarily concerned with clinical activities, the following outcomes were used: (1) number of patients enrolled in Web-based cognitive training activities; (2)

number of new patients enrolled per month; (3) characteristics of the patients enrolled (age, gender, level of education, profession, and medical diagnosis); (4) time to start enrolling patients after initial training visit (months); and (5) number of active clinical centers after 1 year, defined as those centers that have patients under treatment at 1 year.

The outcomes (1) and (2) evaluated clinical network growth and the impact on patient access to cognitive treatments. Linear regression was used to identify any time trend in the number of new patients recruited per month. The outcome (3) was concerned with characterization of patient profiles at the centers, and used to compare the profile of the patients enrolled in the first clinical center (promoter) with that in other centers of the network primarily focused in clinical activities. This comparison was used to assess the global impact of the COGWEB network on the diversity of patients (spectra of age and level of education) and diseases offered supervised Web-based cognitive training. This analysis was performed using Student's *t* test, chi-square, or Fisher's exact tests.

Finally, the outcomes (4) and (5), combined with outcome (2) were used to obtain knowledge on operative network functioning and long-term sustainability. The median time to start enrolling patients was compared among type of center using the Wilcoxon rank test. All the statistical analysis was performed using the SPSS 20.0 statistical package, considering an alpha = 0.05.

Results

Characteristics of the Baseline Centers

The network was initiated in August 2012 with a membership of 16 institutions and 29 health professionals willing to integrate the COGWEB system in their routine (Table 1). These professionals were mainly neuropsychologists and psychologists; two were occupational therapists. The initial centers were all hospital-based clinics, 14 inserted in neurology or psychiatry departments, one in a rehabilitation medicine department, and another in research academic facilities next to a large tertiary center.

Table 1. Major types of centers in the network at baseline and 1 year of follow-up (number of centers, trained professionals, and patients enrolled per major category of center).

	Baseline		1 year		
Centers	Centers	Professionals	Centers	Professionals	Patients enrolled
Clinical					
1. Outpatient clinics in neurology or psychiatry hospital departments[b]	14	25	19	38	209
2. Outpatient clinics in rehabilitation hospital departments[b]	1	2	1	2	2
3. Outpatient clinics in pediatric hospital departments[b]	-	-	1	1	[a]
4. Community day care[c]	-	-	2	3	10
5. Community private practices run by neuropsychologists[c]	-	-	8	8	42
6. Occupational psychology practice in a major company[c]	-	-	1	1	15
7. Psychology office at a second grade school[c]	-	-	1	1	20
Subtotal	15	27	33	54	298
Nonclinical					
8. Academic clinical research[d]	1	2	3	8	163
9. Academic basic research[d]	-	-	1	2	20
10. Postgraduate professional training[d]	-	-	1	1	NA[e]
11. Adult learning institutes[c]	-	-	3	3	60
Subtotal	1	2	8	14	243
Combined total	16	29	41	68	541

[a]The single center in this category was waiting for the initial training visit at the end of study.

[b]Hospital-based

[c]Community-based

[d]Academic/education-based

[e]NA = Not applicable

Characteristics of the Professionals and Centers at 1 Year of Network Functioning

The number of professionals that received specialized training within the network went from 29 to 68 (60 psychologists or neuropsychologists, 4 occupational therapists, 2 neurology residents, 1 psychiatrist, and 1 neurosciences researcher). The mean age of the professionals was 38.1 years (SD 8.8), 83% (57/68) female.

During the first 12 months of functioning, 25 additional centers joined the COGWEB network, from 16 at baseline. There are two of the new centers that have recently joined and were waiting to receive formal training. A total of 41 centers were part of the final analysis. Furthermore, 33 of these centers were classified as clinical (33/41, 80%), while 8 were considered nonclinical and focused in academic research, postgraduate training, or stimulation of normal adults (8/41, 19%) (Table 1).

Considering the services provided by the 25 new centers, 7 belonged to 2 of the initial existing categories (outpatient clinics in neurology or psychiatry departments and academic clinical research centers), and 18 represented 8 new categories of centers (Table 1). At one year, there were 11 different types of centers that could be additionally grouped by major sector of activity as; hospital-based (21/41, 51%), community-based (15/41, 36%), or academic/education-based (5/41, 12%).

From the 39 centers that received training by the end of the study period, 33 (84%) started to use COGWEB, either developing clinical or research activities. Taking into account all the active centers, the median time from the first on-site training visit to the enrollment of the first patient was 1.5 months (interquartile range, 0.5-3.0; SD 1.08 months; 95% CI 1.33-2.15) without differences between types of center (P=.57). Among all clinical centers that received formal training (n=31), by the end of the study period, 80% (25/31; n=25) remained actively enrolling patients and using COGWEB. The 6 clinical centers that were not active at the end of the study (6/31, 19%), never started to enroll patients after their first visit; 1 center was in the first 3 month training period (1/6, 16%), 4 reported organizational and local human resources problems (4/6, 66%), and 1 alleged major technical problems (1/6, 16%). All of the centers that started to use COGWEB with their patients (n=25) were active at the end of the 12 months follow-up period, with no dropouts.

Characteristics of Patients that Received Treatment in Clinical Centers

Among all the 25 clinical centers that started to use the COGWEB system in their activities, a total of 298 patients were enrolled for cognitive training during the first year. The average age was 54.4 years (SD 18.7), 45.3% (135/298; n=135) were female. The patients had diverse formal educational levels, 22.5% (67/298; n=67) from 1-4 years, 28.5% (85/298; n=85) from 5-9 years, 24.8% (74/298; n=74) from 10-12 years, and 24.1% (72/298; n=72) with more than 12 years of school (Table 2). The major causes for cognitive impairment of all the patients treated were; neurodegenerative diseases (115/298, 38.5%; n=115), static structural brain lesions (63/298, 21.1%; n=63), multiple sclerosis and other immune diseases (40/298, 13.4%; n=40), schizophrenia (30/298, 10.0%; n=30), cognitive dysfunction of functional nature (28/298, 9.3%; n=28), attention deficit hyperactivity disorder (12/298, 4.0%; n=12), and others (10/298, 3.3%; n=10) (Table 2).

During the follow-up period there was a significant increase of the number of patients enrolled every month at the clinical network (r=0.6; P= .031) (Figure 2 shows this). At 12 months, 205 patients remained on active treatment (Figure 3 show this).

Table 2. Description of the patients enrolled at promoter center, other clinical centers, and global clinical network.

	Promoter center	Other clinical centers	Global clinical network
Number of patients	117	181	298
Age, years, average (SD)	45.8 (14.7)	60.1 (19.7)	54.4 (18.7)
Gender			
Female frequency, n (%)	39/117 (33.3)	96/181 (53.0)	135/298 (45.3)
Education, years, average (SD)	8.9 (4.2)	10.6 (5.1)	9.8 (4.8)
Cause of cognitive impairment, n (%)			
Neurodegenerative diseases with dementia	20/117 (17.1)	95/181 (52.4)	115/298 (38.6)
Stroke, TBI[a], and other static structural lesions	23/117 (19.7)	40/181 (22.1)	63/298 (21.1)
Multiple sclerosis and other autoimmune diseases	35/117 (29.9)	5/181 (2.8)	40/298 (13.4)
Cognitive dysfunction of functional nature	10/117 (8.5)	18/181 (9.9)	28/298 (9.4)
Schizophrenia	27/117 (23.0)	3/181 (1.7)	30/298 (10.1)
ADHD[b]	1/117 (0.9)	11/181 (6.1)	12/298 (4.0)
Others	1/117 (0.9)	9/181 (5.0)	10/298 (3.4)

[a]TBI = traumatic brain injury

[b]ADHD = attention deficit hyperactivity disorder

Figure 2. Number of patients enrolled each month in Web-based cognitive training through the COGWEB network.

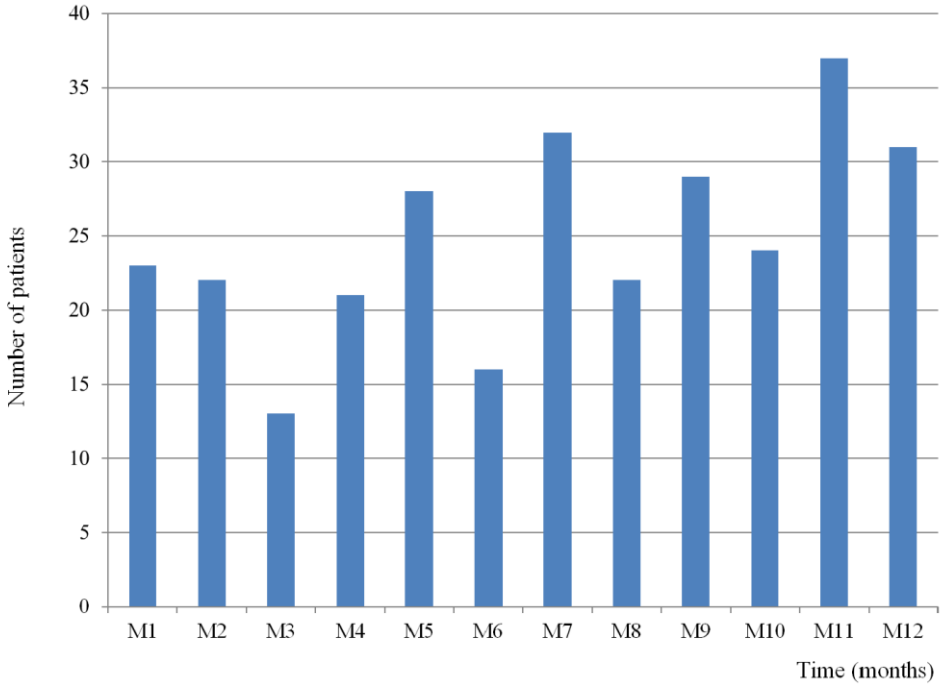
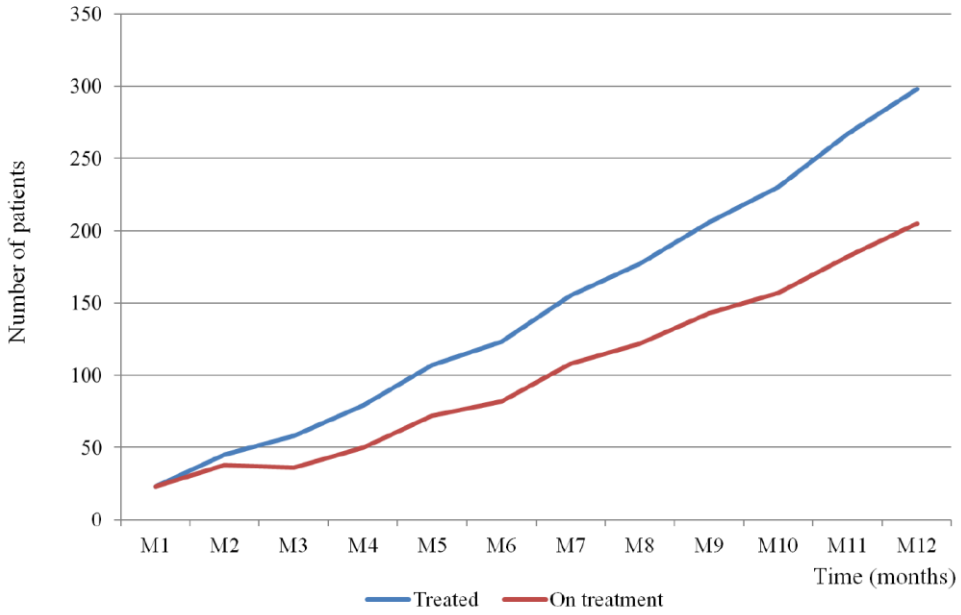


Figure 3. Cumulative number of patients treated during the first year (blue) against the number of patients receiving active treatment trough the COGWEB network each month (red).



Comparison of the First Clinical Center Activity With the Other Network Centers

In Table 2, the patients at the promoter center are compared with the patients at the remaining network, namely: (1) mean age, (2) gender, (3) level of education, and (4) cause of cognitive impairment. The patients recruited at the new network centers were older (P<.001). Nonetheless, the new centers also doubled the proportion of patients with less than 20 years of age 5.6% (10/181) versus 2.6% (3/117) at the promoter center. There was a significant difference in the gender distribution (P=.01), with more males in the promoter center. The patients' educational attainment was higher in the new centers than in the promoter (P=.005). Considering the distribution of the causes of cognitive

impairment, the promoter center enrolled relatively more patients with schizophrenia 23.0% (27/117) versus 1.7% (3/181), *P*<.001, and autoimmune diseases 29.9% (35/117) versus 2.8% (5/181), *P*<.001. Patients with neurodegenerative diseases were the majority of patients enrolled at the new centers (95/181, 52.4%), while their percentage at the promoter center was 17.0% (20/117; *P*<.001). The new centers also enrolled relatively more patients with ADHD, 6.1% (11/181) versus 0.9% (1/117; *P*=.04).

General Description of Activities at Research Centers

Besides the research and development activities occurring at the promoter center, four academic research centers (three clinical and one basic science) participated in the network, using COGWEB in their studies. These centers were dedicated to the study of the effects of cognitive training across several disease models and settings, and looking for molecular, brain imaging, or neuropsychological biomarkers and characterization of neuroplastic processes. Some of the disease models included Alzheimer's dementia, schizophrenia, multiple sclerosis, stroke, and school age learning disabilities. A center was dedicated to epidemiological and public health cohort studies. The total number of patients enrolled in all these research activities during the follow-up period amounted to 417, with 183 (43.9%) coming from studies originating outside the promoter center (Table 1).

Discussion

Principal Findings

Starting from an initial clinical promoter center, integrated in a wider national mental health system setting in Western Europe, it was possible to implement over a 12 month period a collaborative network composed of 41 centers and 68 professionals. This network was dedicated to cognitive intervention and, for its establishment, took advantage of an innovative Web-based cognitive training system, COGWEB [23,24,30]. This tool was developed for clinical and research purposes at the promoter center, and had proved to be proficient in increasing patient access to care and intensity of cognitive training [23-25]. The process of training and sharing a new working tool, and methods, in the field of cognitive training was the cornerstone for the construction of the COGWEB network, and fostered synergies and cooperation between so diverse centers and settings. Health care is a collaborative endeavor, but the degree of collaboration and exchange depends largely on the ability to share and the reciprocity perceived by all the players and stakeholders of a network [10].

The 16 baseline centers that started the network were all based on hospital institutions. Nonetheless, during the first year of functioning, the network was able to attract 25 new centers, and at the end of the study period 11 different categories of centers were identified (Table 1), with 36% (15/41) of them being primarily based on the community. The diversity of centers and institutions enrolled went from referral hospitals and academic centers to day care institutions, schools, adult learning institutes, and companies. All this variety provided us with a wider view on global patient needs, settings, and professional groups interested in improving their standards of care in the field of cognitive intervention. Considering the main characteristics of the national mental health service where the study occurred, namely the range of environments and existing barriers to patient access to cognitive interventions [28,29], this was an important achievement. Only through an inclusive approach is it possible to enhance solutions within a network environment and bridge the gaps between so diverse settings and professionals like those from referral hospital centers, basic and clinical academic centers, or community based institutions [1,8-10]. The needs for cognitive training in the population are very widespread and growing, mostly due to the multiplicity of diseases associated with cognitive deficits, the wide spectrum of ages of onset, and ageing trends in the population [15,27,29]. Altogether, if the aim is a public health impact in the near future, the multiplicity of solutions and settings connected through a cognitive care collaborative network are an important solution to match current and future needs of the population, at the same time improving the sustainability of health services [2,13].

Although the implementation of the clinical network was only a short period of time, the number of patients provided Web-based cognitive training through the network increased steadily, amounting to more than 30 new patients per month in the last two months. Furthermore, the percentage of patients remaining under clinical supervision at the end of the study period was also high (205/298, 68.8%). These multi-center adherence estimates, during a 12 months follow up, may be comparable with adherence data obtained in a previous cohort study at the promoter center (82.8% at 6 months) [25]. Although an indirect quality measure, the reproduction of the adherence data in this study supports the strategy used for the professionals' training at the new centers.

The comparison of the characteristics of patients treated at the promoter center with those enrolled at other centers in the clinical network showed a marked increase, with significant differences, in the diversity of diagnosis, spectra of ages, and education. These findings are in accordance with the different categories of centers and types of services provided within the wider mental health system context [26,29]. The achievement of such a variety of settings and diseases is an important characteristic of the clinical network, namely for the implementation of future research studies and tailoring of the COGWEB system to professional and patient needs. A striking finding was the increase in the number and percentage of patients with neurodegenerative diseases (Table 2), possibly in association with the characteristics of the new centers that adhered to the network, with a great proportion being dedicated to neurodegenerative diseases and elder patients (Table 1). This fact probably reflects the distribution of cognitive impairment in an aging population [31], and the willingness of those centers and professionals to adhere to a network dedicated to Internet cognitive training activities [25].

The strategy defined for professional training, network implementation, and maintenance allowed for a median time to start using the COGWEB system in clinical activities of 1.5 months, with 80% (33/41) of the clinical centers active at 12 months and no dropouts. Nonetheless, 4 institutions reported local organizational and human resources restrictions as reasons for not starting to use the system. These estimates are important for programing further network expansion, anticipating points of tension between individual and organizational goals,

guaranteeing its alignment with financial incentives, and sustainability [9].

Besides clinical activities, it was verified a remarkable growth in research activities over the network. This finding is of utmost importance because studies originating outside the leading promoter center already represented 43.9% (183/417) of patients enrolled in these activities. Research activity is one of the main purposes of this network, and tightly linked to the capacity to generate innovation, processes, and finally patient outcomes [11,32]. This happens in close resemblance with the development of translational research and translational networks in the fields of oncology [6], pediatrics [33], genetics [34], neurodegenerative diseases [35], virology [36], pharmacology [37], big data bioinformatics [38], epidemiology [39], and public health [32], all good examples of the growing efforts being made to fill the gap and speed processes between basic research and clinical outcomes for communities [11].

Limitations

The main limitations of this study are related with the youth nature of the COGWEB network (first year of functioning), being difficult to validate the long term sustainability, outcomes, and impact of the network structure. The differences between center characteristics (41 centers distributed by 11 categories), and the small relative number of patients enrolled at each center prevented us from analyzing patient profiles per type of center and establish comparisons. The aggregation of clinical centers into promoter and others was thus necessary. Data on the severity of patient deficits as well as type, intensity, and quality of cognitive training provided were not analyzed. Additional studies are necessary to evaluate the long term impact of the network on global access of patients to supervised cognitive training at the level of the national health system, quality of care provided, and patient outcomes according to major cause of cognitive impairment. Furthermore, the professional members of the network were not addressed directly through a network survey, nor are data available on key players, ties (indegrees and outdegrees), brokers, or sociograms [6]. These points are very important for translational network analysis, and will be addressed in forthcoming studies on the COGWEB network functioning.

Conclusions

This paper provides insight on the implementation and early outcomes of a large scale multi-organizational cognitive rehabilitation network in a Western European health system environment. Over its first year, there was a major increase in the number, as well as in the clinical diversity, of patients treated and centers, crucial factors for its long term viability. At the beginning of the big data analysis era for neurosciences [40], the consolidation of such a national collaborative network represents an innovative step in mental health care evolution. Furthermore, it may contribute to translational processes in the field of cognitive training and cognitive care, this way providing the foundations for continued innovation, clinical care improvement, and reducing the burden of disease.

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Authors' Contributions

VTC, JP, and PC created the study concept and design. VTC, JP, IA, CM, AS, LR, RB, EC, IAraújo, VB, MC, and COGWEB network collaborators acquired the data. VTC, JP, LR, NR, and PC analyzed and interpreted the data. All authors critically revised the manuscript for important intellectual content. VTC, JP, and PC obtained funding. IA, LR, CM, AS, RB, EC, IAraújo, VB, MC, and COGWEB network collaborators provided administrative, technical, and material support. VTC, JP, VB, MC, NR, and PC provided study supervision.

Conflicts of Interest

VTC and JP have a shareholder position at Neuroinova, Lda, a company that develops and commercializes COGWEB related products. VB and MC received fees for the technological development of COGWEB.

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Abbreviations

COGWEB: Web-based cognitive training system

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Motor training

Article IV – **The vibratory stimulus as a neurorehabilitation tool for stroke patients: proof of concept and tolerability test**

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The vibratory stimulus as a neurorehabilitation tool for stroke patients: Proof of concept and tolerability test

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Abstract. *Introduction*: Current scientific knowledge reinforces that successful reorganization of surviving nervous tissue supports cognitive and motor recovery after stroke. The development of new neurorehabilitation tools to modulate this physiologic process is needed. In this context, vibratory stimuli are a noninvasive form of proprioceptive stimulation of the nervous system and are freely available and easy to use at a low cost.
Objectives: To access the feasibility and tolerability of targeted vibratory stimuli delivered through a wearable device in an early post-stroke setting.
Patients and methods: Five stroke patients were recruited from a stroke unit setting having a first ever medial cerebral artery ischemic stroke with motor deficit. The stimulation device developed delivered external vibratory stimuli to major joints at preprogrammed arrays of intensity, duration and interval of actuation. The tolerability test was set for five-hour duration and during that period data on vital parameters, cognitive, motor and sensitive performance as well as anxiety scores were recorded.
Results: The device remained in place throughout and none of the patients or relatives asked to interrupt the tolerability test. There were no major complications during the trial or the ensuing days. Attention to the affected side during stimulation was increased in four patients, and two were reported as clearly more awake during the test.
Discussion: This is the first tolerability test focused on the use of targeted vibratory stimulus as a neurorehabilitation tool in stroke patients. There were no hazards to report and most interestingly the majority of patients showed increased awareness to the affected side of the body. These findings will be further analyzed under functional MRI control and on long-term ambulatory use trials.

Keywords: Cortical reorganization, neuronal plasticity, proprioceptive stimulation, rehabilitation, stroke, vibratory stimulus

1. Introduction

The most common deficit after a stroke is unilateral motor weakness (hemiparesis), usually combined with a variety of disturbances in sensory afferences and cognitive functioning, such as aphasia, neglect, or depression, that hinder normal rehabilitation programs [1, 15,21,32]. Following injury, the most valuable time-window for rehabilitation is the first three- to six-month period, when brain tissue develops its plastic properties and most functional gains are achieved [3]. Furthermore, it is accepted that the extension of recovery correlates with the intensity of the rehabilitation program followed early after stroke [3,6,23].

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Despite an early phase in understating the process of CNS rehabilitation in human adults, current findings support the development of new interventions, aimed at recovering lost motor function from unaffected neuronal circuits, namely, sensory afferences that can preserve and recover sensitive and motor cortex organization [29]. The ensuing neurological formulations support the development of a stroke therapy based on the intensive delivery of external stimuli.

1.1. Background physiopathological principles

Human beings have sensory skills that develop a structured map of the body and external environment where motor performance takes place. In any interaction there is always an optimization algorithm supported by the neural plasticity and network architecture of the central nervous system (CNS). Maturation of the sensory and motor functions occurs jointly, mounting an integrated architecture between the two and numerous interconnected centers and pathways along the spine, brain stem, thalamus, and cortex [36]. This type of organization makes the system function in a network mode, not as a bidirectional flux of information, which accounts for several advantages, such as the adaptation to new situations and stimuli or the recovery from damage [19].

When injury occurs in the CNS, consequences will result from the location and dimension of damage as well as age because there is a difference if it occurs over an established system or a developing one. The intrinsic mechanisms for reducing neurological damage in an adult subject rely on its network structure, which prevents injuries with total consequences (anesthesia or plegia), and on neuronal plasticity and the possibility for recapitulating part of the maturing process in adulthood, aiding the reorganization of the structures that remain unaffected [19,30]. The network functioning exists both for motor and sensory tasks [7]. However, at the CNS level, it is much more developed for sensory functions [18]. This explains that for the majority of lesion models to the CNS (ischemic or hemorrhagic stroke, trauma), there is usually a greater damage in motor than in sensory functions.

Plasticity of the injured motor cortex depends on the use of the corresponding affected limb [25]. Possibly, neighboring cortex is recruited and compensates for lost motor functions when stimulated. This way, in lesion models, recovery of motor function is necessarily antedated by a reconstitution of the cortical map of the affected side of the body. This phenomenon of cortical remapping is conditioned through stimulation via the preserved sensory afferences [4,27]. When damage occurs in the cortex or thalamus, there is a diminishment of the inhibitory output of these centers on the structures located below. This fact amplifies certain sensory stimuli that previously were not able to evoke cortical stimulation [9]. Therefore, higher placed structures, with a more complex organization, can be reorganized from preserved sensory pathways.

1.2. Stimulus-based neurorehabilitation approaches

Spontaneous recovery is limited after stroke, and the most promising neurorehabilitation therapies have their focus on the repair and restoration of function in the subacute phase. These include device-based approaches, electromagnetic stimulation, and task-oriented repetitive training interventions.

Therapy focused on the repetition of physical tasks (active or passive) is commonly used, but few clinical trials have shown its effectiveness [37]. Additionally, there are very few validated pharmacologic options that improve neurorehabilitation, and trials for new drugs are costly and time consuming [23,33]. High-tech rehabilitation approaches, such as robotic devices and electromagnetic stimulation-based therapeutics, are showing some promising results although at expensive production and operative costs, available only to a very restricted number of patients [20].

Transcranial magnetic stimulation (TMS) aims to modulate a number of functions and behaviors that a damaged CNS cannot provide. Different goals have been pursued, with some studies [12] aimed to increase activity in brain areas showing reduced function after stroke, whereas others focused on reducing activity in brain areas theorized to have a deleterious suppressive effect [11]. Another example is functional electrical stimulation (FES) that has been increasingly used in cases of spinal cord injury [5], cerebral palsy [34], and stroke [38]. However, because of its moderate results, the effectiveness of FES in rehabilitation of stroke patients remains a subject of debate [24].

1.3. Vibration as a stimulus for cortical activation

Much of the existing knowledge relating vibrotactile stimulation and cortical activation derives from preoperative brain scans to ascertain the correct localization of the primary and secondary somatosensory areas (S1 and S2) and the somato-sensory thalamus. Chakrvarty et al. [2] and others [10,13,35] reported robust S1, S2,

and thalamic activations in individual subjects when submitted to vibrotactile stimulation of the hand. These experimental data support the use of vibratory stimulus as a tool for cortical activation. Post-stroke rehabilitation programs also use proprioceptive stimulus and biofeedback techniques to enhance awareness levels toward the side of the body presenting the motor and sensory deficits, mainly in patients with hemi-negligence and anosognosia [22].

Vibration is transduced primarily by Pacinian corpuscles and other deeply situated mechanoreceptors (joint capsule and muscle spindle). The corpuscles have a low response threshold, adapt rapidly to the stimulus and represent 10% to 15% of the cutaneous receptors in the hand [14]. It is possible to potentiate preserved sensory afferences by means of vibratory stimuli as it can be directly applied over major joints or through mechanical noise using low-intensity vibration [26]. This theoretical principle has been demonstrated in several biological systems [8], having already some technical applications [17], although several properties regarding vibration (e.g. amplitude and frequency) and CNS excitability must be better understood.

In this way, a proprioceptive rehabilitation method based on the targeted delivery of vibratory stimuli reveals itself as a promising approach. When compared to pharmacological and high-tech approaches it represents a noninvasive form of stimulation of the nervous system and is rather accessible and easy to assemble in a low-tech affordable rehabilitation device [26,31]. The ultimate objective of this work is to create an intelligent wearable system able to provide continuous vibratory stimulation on the hemiparetic side of the patient in order to test it in a large clinical post-stroke trial.

2. Methods

2.1. Stimulation device

A wearable device was designed and developed for long-term ambulatory use. Its main function is to deliver targeted external vibratory stimuli as a source of proprioceptive input to the CNS. The stimuli can be programmed in intensity, duration, and interval of actuation or can be continuous. Vibratory output is generated by two 12 mm shaftless vibration DC motors [28] (Fig. 1).

As expected with this type of motor, the intensity of vibration is modulated by the input voltage. For example, an input voltage of 3.3V corresponds to a vibratory output with an amplitude of 20 m/s^2 and a frequency of 200 Hz (Table 1). The fixed correlation between amplitude and frequency limits the variety of stimuli available for testing. Nonetheless, this fact is compensated by the increased portability and lower energy consumption of DC motors, which are crucial properties for comfortable ambulatory use.

Table 1
Correlation between vibration amplitude and frequency*

Mode of vibration	Input voltage (V)	Vibration amplitude (m/s^2)	Vibration frequency (Hz)
1	1.2	4	90
2	1.9	9	110
3	2.6	14	165
4	3.3	20	200

*Typical performance characteristics [28].

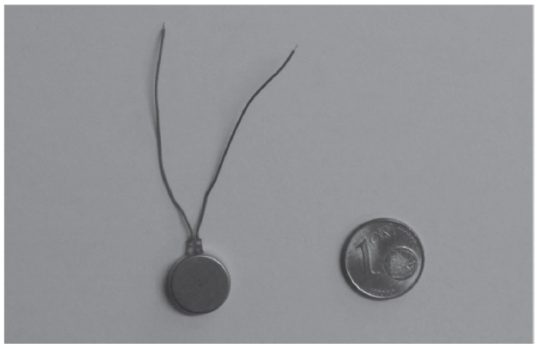

Fig. 1. Vibration motor used (diameter 12 mm, weight 1.3 g).

2.2. Stimulus array

The type of vibratory stimulus delivered was a result of several settings: intensity, duration, and interval between stimuli. In using the prototype features, a number of configurations categorized from A to J (Table 2) were defined for testing. Each configuration was randomly tested in all patients for thirty minutes, with immediate automatic transition between configurations as programmed.

2.3. Patient selection

Patients were selected from the stroke unit upon referral by their stroke physician. They were in an early post stroke period but medically stable, already able to sit and enrolled in a rehabilitation program that included daily periods outside the ward. The recruitment occurred over a one-month period and patients fulfilled all the following criteria:

Table 2
Stimulus combination in amplitude/frequency and timing

Stimulus type	Mode of vibration	Interval of actuation (s)	Stimulus duration (s)
A	1	Continuous	
B	2	Continuous	
C	3	Continuous	
D	4	Continuous	
E	2	5	1
F	3	5	1
G	4	5	1
H	2	30	3
I	3	30	3
J	4	30	3

Table 3
Tolerability test results

Patient number	Age	Gender	Stroke location	NIHSS at admission	Time from stroke onset (days)	Anxiety scale (analogic 0–9)		Complications
						Before	During	
1	55	Male	Left MCA	13	14	1	1	None
2	64	Male	Left MCA	14	12	2	1	None
3	71	Female	Right MCA	12	6	0	0	None
4	43	Male	Right MCA	11	5	3	1	None
5	67	Female	Left MCA	14	7	1	2	None

a) having a first ever medial cerebral artery (MCA) ischemic stroke with a motor deficit defined as a score of at least two points on items five and six of the National Institute of Health Stroke Scale (NIHSS);
b) being previously independent, defined as having a modified Rankin scale (mRS) of 0;
c) without severe aphasia or other cognitive or psychiatric comorbidity that impaired communication.

All patients and caregivers understood the purpose of the study and provided written informed consent. Approval from the referring stroke physician was also obtained prior to enrollment in the experiments. This study was approved by the hospital review board and ethics commission.

Were enrolled five patients with stroke, three male and two female, aged between 43 and 71 years. Three had a left MCA ischemic stroke, and all showed cortical and subcortical involvement on CT/MRI scans. Two patients had visual and sensitive neglect. Motor deficits dominated in all and were severe but were not hemiplegia (NIHSS between 11 and 14). The test occurred between five and 14 days after disease onset.

2.4. Tolerability test design and procedures

The tolerability test was set for five-hour duration and was designed to access easiness of use and comfort provided by the device when applied to the wrist and ankle joints. The experiment took place in a specific area next to the acute stroke unit ward where all monitoring settings, medical and nurse supervision were maintained.

During that period, data on vital parameters, motor and sensitive performance, spontaneous movement quantification, and anxiety scores were recorded. Global awareness and attention to the affected side were assessed through complete neurologic examination before, during, and immediately after the test. A global medical questionnaire and physical examination was recorded and analyzed by the medical staff at the beginning and at the end of the test period.

2.5. Specific measures used

For the patient selection procedure were used the NIHSS and mRS. During the experiment was used an analogical anxiety scale (0–9) to evaluate the stress levels perceived by the patient at baseline and each 30 minutes. For analysis were selected the baseline level and the highest value recorded during the test (Table 3). A standard neurological examination was repeated each 30 minutes, on average, with a special focus on the detection of possible complications like spasticity or dystonia.

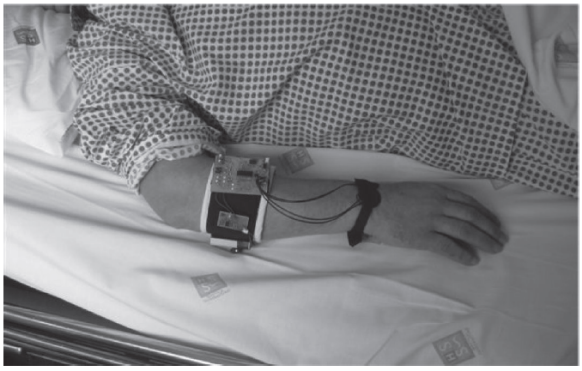

Fig. 2. Tolerability test performed on a stroke patient with an assortment of vibratory stimuli, delivered at the wrist joint.

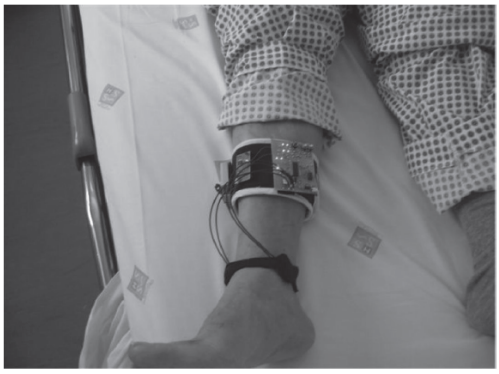

Fig. 3. Tolerability test performed on a stroke patient with an assortment of vibratory stimuli, delivered at the ankle joint.

3. Results

All patients were able to sense and locate tactile and vibratory stimulus on both sides at the beginning of the study. The device remained in place (Figs 2 and 3) throughout the study, and different combinations of vibratory stimuli were administered (differing in intensity, duration, and interval between stimuli) according to a previously determined sequence, as previously described.

None of the patients or relatives asked to interrupt the tolerability test, and there were no records of pain, discomfort, cardiovascular instability, or extreme anxiety. The analogical anxiety scores were low at baseline and did not increase during the experiment except for one patient with a one-point increase in a nine-point scale. Patients were able to sense the stimulus appropriately and discriminate between different intensities and stimulation intervals, either when building up or decreasing. Visual attention toward the affected side immediately upon stimulation was recorded in four patients. A subjective but clear increase in global awareness was recorded in two patients during stimulation, as assessed by the neurologic examination. This finding subsided after the trial. There were no records of dystonia or increased spasticity during the trial or the ensuing days.

4. Discussion

To our knowledge, this is the first tolerability test focused on the use of targeted vibratory stimulus as a neurorehabilitation tool applied to acute stroke patients.

The prototype used remained in place in a ward setting and was energy sufficient during a five hour operation. Despite the long period of consecutive stimulation achieved in all the patients, there were no complications to report during an early post-stroke setting. Most interestingly, the majority of patients increased their attention towards the affected side during stimulation, and two were reported as clearly more awake during the test.

The sample size was very small which constitutes a limitation of this exploratory study. Furthermore there were no data on cortical activation patterns during the various stimulus arrays which hinders any inference on which of the available patterns of stimulation is best. These issues will be addressed further in future studies, under functional MRI control and over intensive daily long-term use, during the ensuing pilot trial to access the efficacy of this neurorehabilitation approach.

Considering our primary goals and the limitations of this study, the present results favor the feasibility of the delivery of vibratory stimuli with the intent to foster cortical remaping through preserved sensory aferences [4,25,26,29,31] in an early post stroke setting. The increased levels of global awareness and attention towards the side of the body may represent an indirect measure of cortical activation [2,10,35], essential for neuroplasticity and modulation of rehabilitation processes [26,29]. These findings may be comparable to what happens with proprioceptive stimulation in hemi-negligence and anosognosia models [22] and justify special attention in the pilot trial.

An important strength of the approach designed and the development of a low cost wearable device is that it can be easily combined with standard therapy in a large number of patients, unlike expensive, high-tech solutions [16,20]. This characteristic will be of great value when conducting a properly sized multicenter case-control study to evaluate this approach.

Acknowledgments

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Motor training

Article V – **A novel system for automatic classification of upper limb motor function after stroke: an exploratory study**

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Technical note

A novel system for automatic classification of upper limb motor function after stroke: An exploratory study

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ABSTRACT

In the early post-stroke phase, when clinicians attempt to evaluate interventions and accurately measure motor performance, reliable tools are needed. Therefore, the development of a system capable of independent, repeated and automatic assessment of motor function is of increased importance.

This manuscript explores the potential of a newly designed device for automatic assessment of motor impairment after stroke.

A portable motion capture system was developed to acquire three-dimensional kinematics data of upper limb movements. These were then computed through an automatic decision tree classifier, with features inferred from the Functional Ability Score (FAS) of the Wolf Motor Function Test (WMFT). Five stroke patients were tested on both sides across five selected tasks. The system was compared against a trained clinician, operating simultaneously and blinded.

Regarding performance time, the mean difference (system vs clinician) was 0.17 s (sd = 0.14 s). For FAS evaluation, there was agreement in 4 out of 5 patients in the two tasks evaluated.

The prototype tested was able to automatically classify upper limb movement, according to a widely used functional motor scale (WMFT) in a relevant clinical setting. These results represent an important step towards a system capable of precise and independent motor evaluation after stroke. The portability and low-cost design will contribute for its usability in ambulatory clinical settings and research trials.

1. Introduction

Proper assessment of motor performance is of major importance for correct decision-making in neurorehabilitation, especially early after stroke [1,2]. This need is shared both by clinical and research settings [1], where competition for specialized human resources limits time dedicated to motor assessment. Moreover, when consecutive evaluations are needed, reproducibility and operator-dependency become important issues [1].

To improve current standards, the development and validation of a wearable system, proficient for automatic assessment of motor function in busy clinical settings is decisive [3]. It could simplify motor assessment and upgrade the management of future rehabilitation plans and clinical trials [4,5].

The research field of wearable quantification tools is currently building momentum, with distinct approaches being proposed [6,7]. One suggestion was the combination of accelerometers with a random Forest classifier, performing multiple repetitions to gather information about within subject variability [8]. Others proposed the use of video tracking systems to acquire kinematics during each task [9,10]. Although feasible, these solutions were expensive and easily affected by visual field occlusions, requiring controlled settings, without background movements. These conditions are difficult to achieve in ordinary busy clinical sceneries.

Abbreviations: FAS, Functional Ability Score; MARG, magnetic angular rate and gravity; MDC, minimal detectable change; WMFT, Wolf Motor Function Test.

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To further study our approach, we selected the Wolf Motor Function Test (WMFT), a widely used scale. It is composed of several tasks organized in growing complexity, from proximal to distal joint assessment, ending with a global upper limb movement evaluation [11,12]. Furthermore, it is easy to use, provides information that can orient contemporary functional rehabilitation strategies and has been extensively studied in stroke patients [13,14].

The aim of this study was to develop and evaluate a portable system, designed to provide independent, real-time, automatic classification of upper limb function, according to selected items of the WMFT. The relevant environment chosen was an outpatient stroke clinic.

2. Methods

2.1. Motion capture system

The core element is a movement quantification system that allows for a continuous analysis regarding a user's kinematic data (Fig. 1). The design of the underlying motion capture method was based only on magnetic, angular rate and gravity (MARG) sensors [3]. Data were stored on an SD card, communication handled by a Bluetooth module and power supplied by a 3.7 V lithium battery charged using a USB connection [3]. These set of options increased the portability of the system (Fig. 1) that could be integrated in a low-cost wearable device capable of continuously monitoring motor function in ambulatory mode and was already tested in clinical experiments [15,16].

The system was structured according to three main blocks [3,16]:

(1) A sensor fusion algorithm in each one of the four quantification modules (Q1–4, Fig. 1), developed to estimate the kinematics of rotation of the body-frame in relation to the earth-frame, combining independent measures from three-axis gyroscope, accelerometer and magnetometer (angular velocity, linear acceleration and magnetic alignment). This minimized errors on the orientation of each module within our human kinematics model [3].
(2) The human kinematics model that incorporated the rotation perceived in each module with a biomechanical model configuration for the human upper limb (Fig. 1c), focused on the estimation of the three-dimensional orientation and position of two body segments (arm and forearm vectors) and three major joints (shoulder, elbow and wrist) [16].
(3) An upper limb motor function evaluation block (Figs. 1b and 2) that parameterized features of movement (e.g., acceleration, velocity, amplitude, execution paths, smoothness) to achieve a correct clinical classification (e.g., irregularities of tonus, rhythm or velocity, spatial deviations, synergies, fatigue) [3,15]. It compared motion dynamics of a specified task with the quality metrics of reference previously set by: clinical prescription, execution parameters from the normal side of the body, or data from a population of reference [15,16].

The wearable system was designed to evaluate upper limb motor function on both sides of the body (Fig. 1c). As an example, for the evaluation of the affected side, three wireless modules (Q1–3) were placed at the wrist, arm and shoulder (exactly over the acromio-clavicular joint) of the impaired side of the patient (ipsilesional) and an extra module (Q4) was located at the wrist of the contralesional side. The reverse setting was used to collect data from the normal side of the patient. Data from each module was acquired at a 50 Hz rate and sent wirelessly to a laptop computer.

Each limb segment corresponded to a translational 3D vector in a kinematic model, e.g., the left arm was represented by the vector $\boldsymbol{L}Arm$, the left forearm by $\boldsymbol{L}Forearm$, and the shoulder segment by $\boldsymbol{L}Shoulder$. The length of each segment was specified according to normalized dimensions (arm length was 1, shoulder and forearm were ratios). To calculate these parameters, anthropometric dimensional data of a 40-year-old American male (95th percentile) were followed [17].

The rotation of each vector in space was accomplished with the dot product between the initial vector ($\boldsymbol{L}Shoulder_{Init}$, $\boldsymbol{L}Arm_{Init}$ or $\boldsymbol{L}Forearm_{Init}$), the quaternion representing the actual orientation of the limb (q_s, q_E or q_{Wi}) and its conjugate (q_s^*, q_E^* or q_{Wi}^*).

$$\boldsymbol{L}Shoulder_{\boldsymbol{Update}} = q_s \cdot \boldsymbol{L}Shoulder_{Init} \cdot q_s^* \quad (1)$$

$$\boldsymbol{L}Arm_{\boldsymbol{Update}} = q_E \cdot \boldsymbol{L}Arm_{Init} \cdot q_E^* \quad (2)$$

$$\boldsymbol{L}Forearm_{\boldsymbol{Update}} = q_{Wi} \cdot \boldsymbol{L}Forearm_{Init} \cdot q_{Wi}^* \quad (3)$$

The current 3D positions of the shoulder (P_S), elbow (P_E) and ipsilesional wrist (P_{Wi}) were calculated by adding the above translational vectors with the respective starting point of each segment. The point V_0 was the model origin and therefore static.

$$P_S = V_0 + \boldsymbol{L}Shoulder_{\boldsymbol{Update}} \quad (4)$$

$$P_E = P_S + \boldsymbol{L}Arm_{\boldsymbol{Update}} \quad (5)$$

$$P_{Wi} = P_E + \boldsymbol{L}Forearm_{\boldsymbol{Update}} \quad (6)$$

Knowing these three points, the kinematics model could replicate any tri-dimensional movement performed by the patient's ipsilesional upper limb. The position of the contralesional wrist (P_{Wc}) was used to evaluate whether the uninvolved extremity participated in the motor task, and was calculated applying the dot product between the static vector $\boldsymbol{R}Forearm_{Init}$ and the respective quaternion (q_{Wc}).

$$P_{Wc} = q_{Wc} \cdot \boldsymbol{R}Forearm_{Init} \cdot q_{Wc}^* \quad (7)$$

This solution optimized the clinical procedure, reducing the operative complexity and time to collect data. Furthermore, it provides the backbone for a motion normative database, since all kinematics produced by different users are suitable for a direct comparison.

2.2. Upper limb motor function evaluation

The first approach to motor function assessment was implemented over a subset of the 15 motor tasks of the WMFT [18,19]: forearm-to-table (task 1), forearm-to-box (task 2), extend-elbow (task 3), hand-to-table (task 4) and hand-to-box (task 5). Each task was evaluated according to performance time (seconds) and Functional Ability Score (FAS) [19].

To measure performance time, the system determined two markers for each task. Onset of movement was identified when the absolute velocity of one of the quantification modules exceeded 2% of peak velocity, after being below this threshold for at least 1 s [3,15,16]. End of movement was then determined as the moment when velocity resumed to zero for at least 1 s. The time window of movement analysis was set to 1 s because lower values could lead, in case of a non-smooth movement, to prematurely determine its end [3,15,16].

For FAS analysis, tasks 1 and 2 were chosen to test the proficiency of the system in the automatic assessment of the motor deficit. This was done according to the WMFT criteria and specific guidelines provided for scoring functional ability of movement [19]. For example, an FAS of 3 is achieved if in the unilateral motor task the "*Arm does participate, but movement is influenced to some degree*

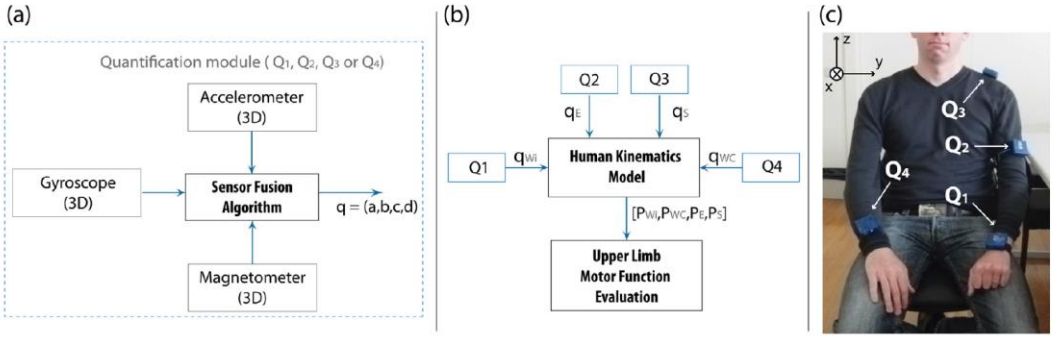

Fig. 1. (a) Each quantification module (Q1–Q4) retrieves the information regarding the rotation performed through the fusion of the independent measures of the three-axis gyroscope, accelerometer and magnetometer. (b) The global system is composed of two main blocks: the motion capture system (human kinematics model and quantification modules) and the upper limb motor function evaluation system. (c) A user wearing the motion capture system.

by synergy or is performed slowly and/or with effort". This guideline was streamlined into the following decision tree (Fig. 2a) and incorporated in the automatic assessment system.

2.2.1. Automatic decision tree features

Data were collected on both sides, first on the normal and then on the affected side. Furthermore, when in place, modules Q1–4 detected movement on either side, namely any simultaneous or synergic movements (Fig. 1). For each motor task, movement was scrutinized according to five features (Fig. 2b). It was considered complete if executed in less than 120 s as required by WMFT specifications [20]. Synergy with the ipsilesional shoulder was associated with a movement performed slowly and with effort. To account for near normal movements in tasks 1 and 2 (normally executed in the yz plane of motion), motor performance was only considered normal if displacement in the x-axis was inferior to 30° [3,15]. These features were detailed for the two tasks and not meant to be applied to the analysis of all the 15 tasks of the WMFT.

To identify the occurrence of synergic movement of the shoulder joint (D in Fig. 2b), the distance S_S, computing the length of the path of the shoulder joint from its initial to the final position, was determined. We included the analysis of the three-dimensional pathway, as synergy could take place in any dimension of movement [3,16].

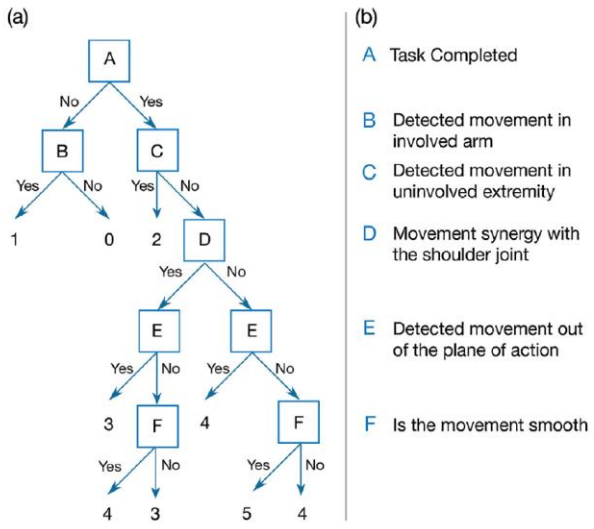

Fig. 2. (a) Decision tree classifier used to evaluate each motor task (0–5) according to FAS of WMFT. (b) Description of the decision tree features (A–F) concerning tasks 1 and 2 of the WMFT.

$$s_S = \int_{t_0}^{t_f} \sqrt{\left(\frac{dP_{Sx}}{dt}\right)^2 + \left(\frac{dP_{Sy}}{dt}\right)^2 + \left(\frac{dP_{Sz}}{dt}\right)^2}\, dt \tag{8}$$

The scalar metric S_S was compared to the baseline acquired from the analysis of movement performed in the contralesional side. The movement was considered synergic with the shoulder joint if the length of the path of the ipsilesional shoulder surpassed 100% of the value obtained for the contralesional side. The proposed ratio was given by α, which increases with shoulder displacement on the affected side.

$$\alpha = \left(\frac{S_{S(ipsi)} - S_{S(contra)}}{S_{S(contra)}}\right) \cdot 100 \tag{9}$$

In what concerns movement out of the plane of action (E in Fig. 2b), and considering that tasks 1 and 2 were performed in the yz-plane, displacement of the path of the elbow joint out of the x-axis origin was calculated. This way, the movement was correctly performed if $P_{Ex}(n) \approx P_{Ex}(0)$, $\forall n \in N$ and $s_{Ex} \approx 0$.

$$s_{Ex} = \int_{t_0}^{T} \left|\frac{dP_{Ex}}{dt}\right| dt \tag{10}$$

The binary threshold of feature E was determined in relation to a maximum deviation of 30° relative to the origin [3,16]. In this way, since the human kinematics model specified the arm segment with a length of 1 and for the task to be complete the user should return to the (x-axis) origin, the movement was determined out of the plane of action if:

$$s_{Ex} \geq 2 \cdot l \cdot \sin\,\theta_{\max} \tag{11}$$

$$s_{Ex} \geq 1 \tag{12}$$

where l is the length of the arm segment (reference value of 1) and θ_{max} is the maximum deviation possible of the arm segment in relation to the x-axis origin.

To quantify the smoothness of movement (feature F from Fig. 2b), we used the jerk metric since it showed higher correlation between changes in smoothness and the Fugl-Meyer score [21]. The jerk metric was first introduced by Flash and Hogan [22] and redefined by Hogan and Sternad [23] as:

$$jerk = \frac{\left(\int_{t_0}^{t_f} \left(\frac{d^3P_{Wx}}{dt^3}\right)^2 + \left(\frac{d^3P_{Wy}}{dt^3}\right)^2 + \left(\frac{d^3P_{Wz}}{dt^3}\right)^2 dt\right) T^5}{S_w^2} \tag{13}$$

$$s_W = \int_{t_0}^{t_f} \sqrt{\left(\frac{dP_{Wx}}{dt}\right)^2 + \left(\frac{dP_{Wy}}{dt}\right)^2 + \left(\frac{dP_{Wz}}{dt}\right)^2}\, dt \quad (14)$$

$$T = t_f - t_0 \quad (15)$$

where t_0 and t_f are the time samples that respectively represent the beginning and end of the motor task performed.

This new formulation defines the jerk metric as a dimensionless measure of smoothness, consequently eliminating any dependence on performance time or amplitude of execution verified in previous studies [10,21,22].

The decision threshold of feature F was defined as for feature D. If the jerk value retrieved from the analysis of the ipsilesional motor execution (tasks 1 or 2) exceeded 200% of the value obtained from the contralesional movement, the motor execution was decided as non-smooth [3,16]. The proposed ratio was given by β.

$$\beta = \left(\frac{jerk_{(ipsi)} - jerk_{(contra)}}{jerk_{(contra)}}\right) \cdot 100 \quad (16)$$

The value for each binary threshold (S_{Ex}, α and β) was defined in accordance with our clinical partners, from an empirical perspective, through repeated testing of the system in a laboratory environment and previous studies [3,15,16]. Linear and angular accuracy for motion detection were previously assessed in a laboratory setting (hand-to-mouth task, normal subjects) by comparison with an optical sensor system (Vicon, Oxford, UK) and agreement rates were between 0.98 and 1 [16].

2.3. Subjects

The system was tested in a regular outpatient stroke clinic setting. Five male patients, aged between 35 and 73 years old, all right handed were selected. All patients had suffered a medial cerebral artery ischaemic stroke, were already medically stable, able to sit and stand and had upper limb motor impairment (three on the right side), but hemiplegia was not allowed (able to actively extend wrist, thumb, and at least 2 other digits >10°). Their motor performance, on the impaired limb, ranged from a near normal status (patients 1 and 2) to moderate functional deficit (patients 3–5). Cognitive performance was reported as normal in all patients according to clinical assessment with relatives and mini mental state examination [24]. Prior to testing, patients and caregivers were asked to give written informed consent as approved by the local Ethics Committee.

2.4. Test description

Patients received a brief explanation of the five tasks selected and were requested to perform them, first with the normal side and then with the impaired side. Only one trial per patient, on each side, was analyzed for all tasks, to reproduce the usual clinical setting. The clinician was proficient in the WMFT and was asked to independently score the movement according to the WMFT guidelines being allowed to review the video recordings of the test later on (ideal clinical scenery). The automatic movement quantification system operated simultaneously, but neither the clinician nor the patients were allowed to know the results during the assessment.

2.5. Statistics

The SPSS software was used. For the description of the time variables, the mean and standard deviations were used. To describe the difference in the performance time reported by the clinician compared with that obtained by the automatic system, the modular difference between the two was calculated. The related-samples Wilcoxon ranked test was used for comparing the values obtained by the two methods within each task.

3. Results

3.1. Performance time

The comparison of the measures acquired by the clinician with those achieved by the proposed system, using the modular difference between the two, depicted a mean of 0.17 s and a standard deviation of 0.14 s (Fig. 3a). The system retrieved lower values of time in 20 of the 25 assessments and equalled the clinician in 4.

All the five tasks analyzed are different, and have specific completion times. For each task, there was a set of five paired values, corresponding to the assessments performed by the clinician and the system in each one of the five patients. A related-samples Wilcoxon ranked test was used. There were no statistically significant differences between the clinician and the system in task 1 ($P = 0.07$), task 2 ($P = 0.07$), task 3 ($P = 0.26$) and task 5 ($P = 0.07$). In task 4 we found a P of 0.04.

3.2. Functional Ability Score

All patients were able to complete tasks 1 and 2 without using the uninvolved extremity and features A, B and C were respectively classified as Yes, Yes and No for all subjects.

For feature D, Table 1 shows the length of the three-dimensional path of the shoulder in both tasks for the five subjects. Subject 3 in tasks 1 and 2, and subject 4 in task 2 were clearly identified as moving with the aid of the shoulder.

The decision of feature E is shown in Table 2 where subjects 3, 4 and 5 for task 1 and subjects 3 and 5 for task 2 showed deviation out of the x plane of motion.

The decision regarding the smoothness of movement (feature F), based on the dimensionless jerk metric, demonstrated a higher discrimination sensitivity between an ipsi- and a contralesional movement. Both subjects 3 and 4 exhibited non-smooth movements for tasks 1 and 2 (Table 3, Fig. 3c).

A comparison between scores estimated by the clinician vs the automatic system, based on the features depicted in Tables 2 and 3, is shown in Fig. 3b.

4. Discussion

The introduction of new tools for automatic classification of motor function using quality kinematic variables of movement has been demonstrated to be useful in common clinical practice [25]. This could save time and improve accuracy due to the analysis of the movement in all its three dimensional projections [26,27].

The present study provided data on the validity of a new portable motion capture system based on MARG measures to estimate the result of a clinical score test and performance time. This was accomplished in a relevant clinical environment (outpatient stroke clinic) in real time and with a high rate of agreement with the clinician. To our knowledge, this was achieved for the first time.

The analysis of the performance time revealed a very small mean difference (0.17 s), probably related to a clinician delay in determining the exact moment of task completion (systematic overtime). Although this study is probably underpowered, the difference between measures only achieved statistical significance in task 4 (hand-to-table), the shortest tasks of the WMFT. The human evaluation of performance time in the WMFT has a standard error of measurement of 0.2 s and a minimal detectable change (MDC) of 0.7 s [28]. When evaluating performance time in the shortest tasks

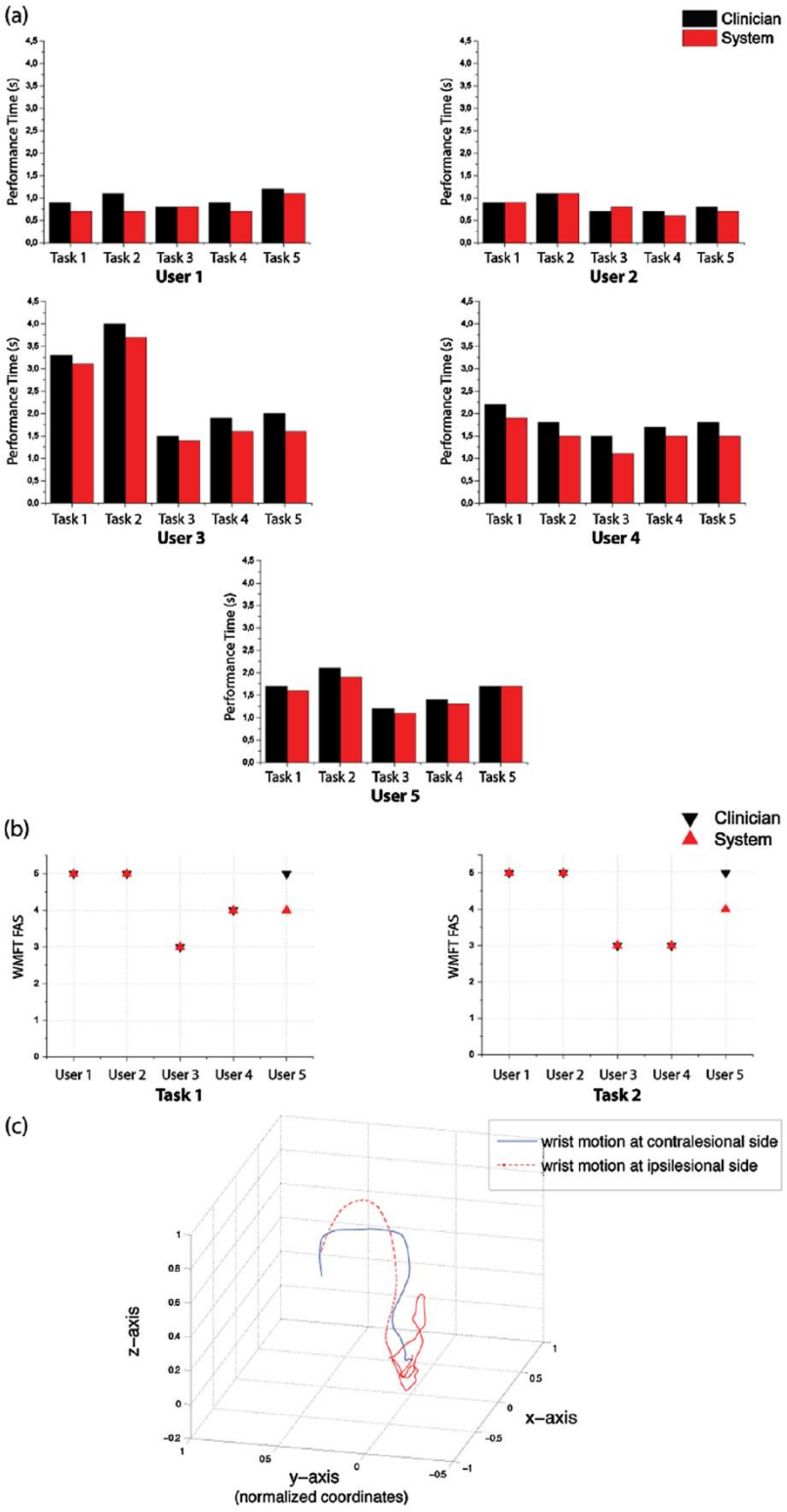

Fig. 3. (a) Performance time as measured automatically by the system or obtained by the clinician in all patients and tasks. (b) FAS scores for the 5 patients in task 1 (forearm-to-table) and task 2 (forearm-to-box). (c) Three dimensional wrist kinematics relative to subject 3 when performing task 1, detailing the movement of the upper limb from its resting position at the upper leg to the table.

Table 1
Feature D metrics (3D path of the shoulder segment S_S).

Subject	Contralesional side[a] (task 1)	Ipsilesional side[a] (task 1)	α (%)	Feature D	Contralesional side[a] (task 2)	Ipsilesional side[a] (task 2)	α (%)	Feature D
1	0.21	0.19	−10	No	0.28	0.29	4	No
2	0.29	0.31	7	No	0.27	0.31	15	No
3	0.25	1.06	324	Yes	0.27	0.73	170	Yes
4	0.32	0.51	59	No	0.33	0.71	115	Yes
5	0.33	0.43	30	No	0.22	0.29	32	No

[a] Normalized dimensions.

Table 2
Feature E metrics (elbow out of the x-axis origin).

Subject	Contralesional side[a] (task 1)	Ipsilesional side[a] (task 1)	Feature E ($S_{Ex} > 1$)	Contralesional side[a] (task 2)	Ipsilesional side[a] (task 2)	Feature E ($S_{Ex} > 1$)
1	0.17	0.23	No	0.24	0.31	No
2	0.22	0.31	No	0.18	0.35	No
3	0.36	1.81	Yes	0.19	1.59	Yes
4	0.6	1.45	Yes	0.08	0.51	No
5	0.27	1.2	Yes	0.45	1.22	Yes

[a] Normalized dimensions.

Table 3
Feature F metrics (dimensionless jerk).

Subject	Contralesional side[a] (task 1)	Ipsilesional side[a] (task 1)	β (%)	Feature F	Contralesional side[a] (task 2)	Ipsilesional side[a] (task 2)	β (%)	Feature F
1	1.03×10^7	8.98×10^6	−13	Yes	5.31×10^6	6.27×10^6	18	Yes
2	4.27×10^6	5.32×10^6	25	Yes	3.57×10^6	4.25×10^6	19	Yes
3	3.78×10^7	7.68×10^8	1931	No	4.94×10^7	2.20×10^8	345	No
4	1.62×10^7	2.58×10^8	1492	No	3.75×10^7	1.07×10^8	185	No
5	4.39×10^7	5.23×10^7	19	Yes	2.13×10^7	2.66×10^7	25	Yes

[a] Normalized dimensions.

or subsets of patients with faster performances, the device proposed may improve MDC. This point favours the use of automatic assessment in clinical trials or during the collection of normative data of motor recovery in stroke patients, nonetheless further studies are needed.

In what concerns the results of FAS estimation (tasks 1 and 2), the system and the clinician agreed in 4 out of 5 participants. Beforehand there were expectations that the system might be sensitive enough to details of motor performance not currently detected by the clinician when reviewing the video. In fact, that appears to happen for subject 5 in both tasks, where the system detected that the user performed the movement out of the plane of action. This type of analysis is somewhat difficult to accomplish using a two-dimensional view of the movement, which is the case of the clinician when examining the video of the session. The features presented in Fig. 2 are specific for tasks 1 and 2. In order to evaluate the other three motor tasks (tasks 3 to 5) and thus expand the system, new metrics with higher discrimination thresholds for each specific task must be introduced. Taking task 3 as an example, elbow extension ideally occurs in the xy-plane of motion. A specific new metric would be required to quantify movement of the wrist on the z-axis. The evaluation of features D and F, based on the comparative analysis between ipsi- and contralesional sides, can be much improved if normative data from larger samples are incorporated in the analysis (optimizing ratio thresholds for α and β). This would empower the system with better discriminating capability in each category.

Most interestingly, it has been demonstrated that the WMFT can be successfully streamlined from 17 to 6 tasks (hand-to-table, hand-to-box, reach-and-retrieve, lift-can, lift-pencil and fold-towel) [29,30]. In this way, the combination of the present system with a kinematic glove for hand function might allow for the comparison of the two methods.

4.1. Study limitations

This experiment was an exploratory study in a small sample of ambulatory stroke patients and a restricted number of WMFT tasks. Participants were all outpatients and preserved high level of motor capacity. The use of this system in patients with severe motor deficits will be approached in future studies.

5. Conclusions

The prototype tested was able to correctly determine the performance time of each of the motor tasks assessed. Furthermore it reproduced the FAS of the WMFT in the two tasks assessed, when compared against clinical scores obtained after video revision. Although further studies are needed, aimed at, among others, the acquisition of normative data and validating decision trees for other important tasks, this tool can improve the quality of data and consequently clinical decision-making in stroke rehabilitation plans.

An automatic system based on normalized data and evaluated using a quantitative method represents a clear evolution in relation to the traditional assessment of motor performance centred solely on human observations.

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Competing interests

The authors declare that they have no competing interests.

Ethical approval

The study was approved by the local ethics committee (CHEDV, Feira, Portugal).

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Motor training

Article VI – **Motor task performance under vibratory feedback early poststroke: single center, randomized, cross-over, controled clinical trial**

Cruz VT, Bento V, Ruano L, Ribeiro DR, Fontão L, Mateus C, Barreto R, Colunas M, Alves A, Cruz B, Branco C, Rocha NP, Coutinho P

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Motor task performance under vibratory feedback early poststroke: single center, randomized, cross-over, controled clinical trial

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Stroke rehabilitation is far from meeting patient needs in terms of timing, intensity and quality. This study evaluates the efficacy and safety of an innovative technological tool, combining 3D motion analysis with targeted vibratory feedback, on upper-limb task performance early poststroke (<4 weeks). The study design was a two-sequence, two-period, randomized, crossover trial (NCT01967290) in 44 patients with upper-limb motor deficit (non-plegic) after medial cerebral artery ischemia. Participants were randomly assigned to receive either the experimental session (repetitive motor task under vibratory feedback and 3D motor characterization) or the active comparator (3D motor characterization only). The primary outcome was the number of correct movements per minute on a hand-to-mouth task measured independently. Vibratory feedback was able to modulate motor training, increasing the number of correct movements by an average of 7.2/min (95%CI [4.9;9.4]; $P < 0.001$) and reducing the probability of performing an error from 1 : 3 to 1 : 9. This strategy may improve the efficacy of training on motor re-learning processes after stroke, and its clinical relevance deserves further study in longer duration trials.

Unilateral motor weakness (50–83%) and cognitive impairment (50%) are the most common deficits resulting from stroke and the main causes of disability[1–6]. Early rehabilitation, within the first three to six months, is crucial in increasing the probability of a good functional outcome[7–9] and currently perceived as an essential part of effective stroke care[3,10]. However, the type of interventions, when they should begin, how intensive and for how long they should occur all remain unanswered questions and are currently the focus of research in the field[11].

Spontaneous recovery or pharmacologically triggered neuroplasticity have shown no significant effect in reducing functional disability after stroke[7,8,12] which renders motor recovery largely dependent on rehabilitative interventions mediated by specialized health professionals in institutional environments[13]. However, the availability of effective poststroke rehabilitation treatments is far from meeting the needs of all stroke patients in due time, intensity, quality or duration[3,14,15]. Moreover, even patients that achieve functional independence after stroke are at increased risk of developing long-term disability, independently of recurrent stroke or other risk factors[16,17].

To overcome these complex problems, new technological tools and rehabilitation approaches are being developed and tested[3,11,13,18–22]. In addition to the intensity of the rehabilitation[23], its quality and timing as well as the dose and monitoring the possible adverse-effects of these interventions are of increasing importance in early poststroke management[11].

Over the last few years we have developed a low cost technological tool designated as Stroke Wearable Operative Rehabilitation Device (SWORD)[24] that allows for controlled prescription of specific motor tasks in training sessions supervised by a health professional. The SWORD device combines targeted vibratory feedback[25],

over the major upper or lower limb joints, with wearable 3D vectorial continuous movement quantification analysis[26]. The training sessions using the device can be controlled at distance and occur complementary to the current institutional-based programs, either at the institution or remotely supervised at home[13].

The aim of this study was to explore the efficacy and safety of the SWORD device (vibratory feedback and 3D motor quantification) and to determine its effect on the quality of movement during the first training session of inpatients in an early poststroke phase.

Results

From May to October 2013 a total of 164 patients having had their first stroke were assessed for eligibility (Figure 1). A total of 120 were excluded. Among these, 116 did not meet criteria and 4 declined to participate. The primary reasons for non-inclusion were the type of stroke (n = 56), the severity of the deficits (n = 20) and logistic or acute phase treatment related issues that precluded enrollment within the first 4 weeks (n = 33). A total of 44 participants were included and 22 were randomized to each study arm. All participants were able to complete the cross-over experiment on both sides. On the study arm that performed the active comparator session first, one patient was excluded from the analysis due to technical problems that led to the loss of data during the experiment on the normal side of the body. On the study arm that performed the experimental session first, one patient was excluded after revising the discharge diagnosis given by the stroke unit. The analysis of data was conducted in 43 participants on the paretic side and 42 participants on the normal side (Figure 1).

The mean age of the participants was 66.5 years (SD = 13.1; range 44–92 yrs), 39.5% were female, the average educational level was 4.1 years (SD = 2.4; range 0–9 yrs) and the average time from stroke onset to enrollment was 6.8 days (SD = 7.3; range 3–27 days). Stroke etiology was cardioembolic (30.2%), small vessel disease (20.9%), large vessel disease (11.6%), multiple causes (30.2%) and other causes (7%). The median national institute of health stroke scale (NIHSS) at randomization was 4.0 (IQR [3.0;6.0]), 37.2% had a modified Rankin scale (mRS) score of 1or 2 and 60.5% a mRS score of 3 or 4. The baseline characteristics of each allocation group are presented in

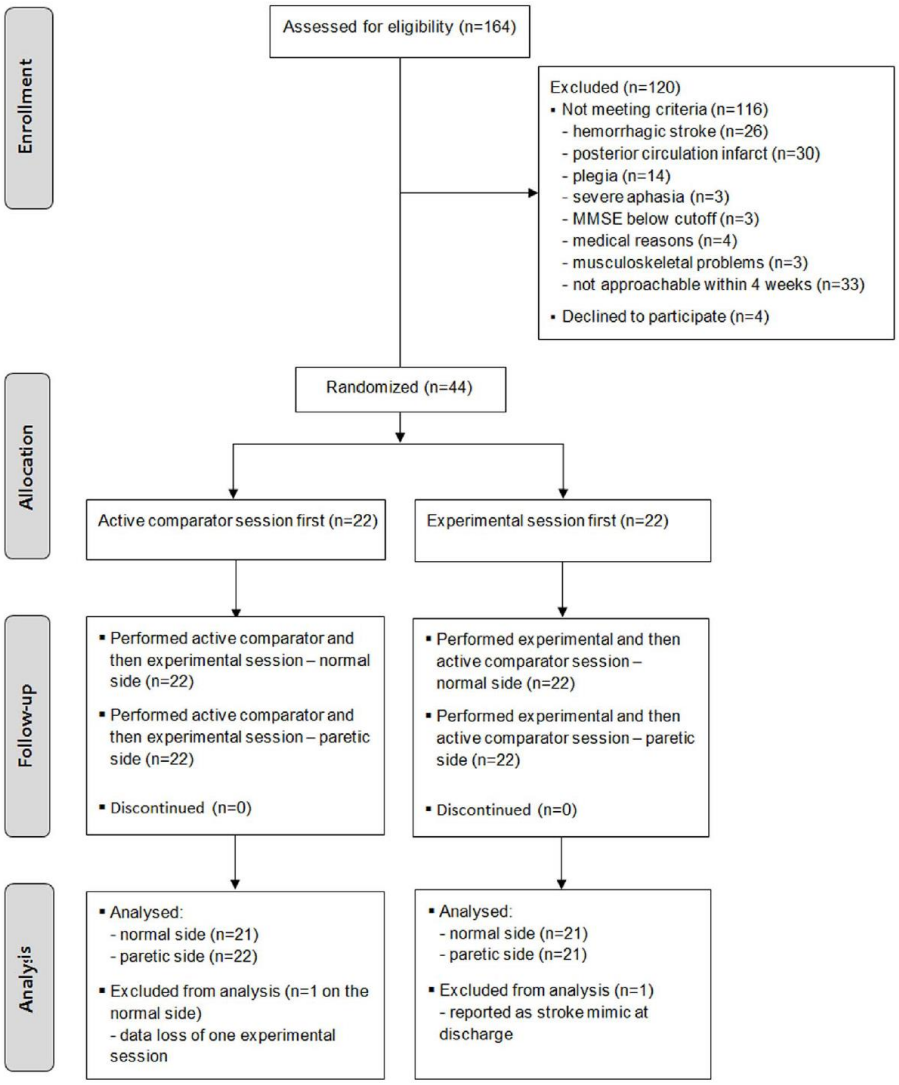

Figure 1 | Study flowchart and CONSORT diagram.

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Table 1 | Characteristics of participants in the study

	Active comparator first	Vibratory feedback first	*P* value
Number of patients	21	22	
Age *years, average (SD)*	64.9 (12.0)	68.2 (14.3)	0.42†
Gender *female frequency*	40.9%	38.1%	0.85§
Education *years, average (SD)*	4.6 (1.8)	3.7 (2.9)	0.21†
Handedness *Right side frequency*	100%	100%	NA
Stroke side *Right side frequency*	54.5%	52.4%	0.88§
Stroke type OCSP (%)			
TACI	4.5	9.5	
PACI	63.6	61.9	
LACI	31.8	28.6	0.81‖
Time from onset *days, average (SD)*	6.2 (6.8)	7.5 (7.9)	0.55†
NIHSS admission *median [IQR]*	3.0 [1.0;6.0]	4.0 [1.0;6.0]	0.85‡
Motor NIHSS* admission *median [IQR]*	3.0 [3.0;9.0]	3.0 [3.0;9.0]	0.85‡
Baseline functional status at the time of randomization			
Barthel *median [IQR]*	60 [45;90]	60 [50;85]	0.82‡
Rankin (%)			
1	18.2	14.3	
2	13.6	28.6	
3	18.2	28.6	0.31‖
4	50.0	23.8	
5	0	4.8	
NIHSS *median (IQR)*	4.5 (3.0–7.3)	4.0 (3.0–6.0)	0.84‡
motor NIHSS* *median [IQR]*	2.5 [0;3.0]	3.0 [0;4.0]	0.86‡
Neglect *neglect frequency*	22.7%	23.8%	0.93§

OCSP - Oxford community stroke project (stroke classification); TACI – Total anterior circulation infarct; PACI – Partial anterior circulation infarct; LACI – Lacunar anterior circulation infarct; IQR – interquartile range;
*Sum of the scores of the items 4, 5a, 5b, 6a and 6b.
†Independent samples T test,
‡Mann–Whitney U test,
§qui-squared test and ‖ Fisher exact test.

Table 1. There were no significant imbalances between groups with respect to gender, education, stroke type, side, severity, frequency of neglect or time from onset.

All patients were able to complete the hand-to-mouth sessions prescribed with no interruption due to fatigue, pain or any medical condition, both in the normal and the paretic side trials. The average duration of each session on the normal side was 3.2 min (SD = 1.6; range 1–10 min) and on the paretic side was 2.9 (SD = 1.7; range 1–10 min). The average amplitude, on the sagittal plane, required to consider the hand-to-mouth movement as correctly done was 31.0 degrees (SD = 10.3; range 12–50°) on the normal side and 26.8 (SD = 11.0; range 12–50°) on the paretic side.

Primary end point. In the trial for the paretic side, the average number of correct movements was 25.7 per min (SD = 11.7; 95% CI [22.1;29.3]) during the experimental session (vibratory feedback on) and 18.5 correct movements/min (SD = 11.4; 95% CI [14.9;22.0]) in the active comparator session (Figure 2A). The number of movements made on the patient's affected side in the experimental session increased by an average of 7.2 correct movements/min (SD = 7.4; 95% CI [4.9;9.4]) compared to the active comparator session ($P < 0.001$). This difference corresponds to a relative increase average of 2.8 more correct movements per minute in the experimental session (SD = 5.3; 95% CI [1.2;4.4]; $P < 0.001$). In 93% (40/43) of the patients there was an increase in the number of correct movements performed per unit of time during the experimental session (Figures 2B and 2C).

For the trial performed on the normal side, the average number of correct movements was 30.3 correct movements/min (SD = 14.6; 95% CI [25.7;34.9]) during the experimental sessions and 23.6 correct movements/min (SD = 14.2; 95% CI [19.2;27.9]) in the active comparator session (Figure 2A). Analysing the effect size in the experimental session, the number of movements increased an average of 6.7 correct movements/min (SD = 7.8: 95% CI [4.2;9.1]) compared to the active comparator session within each subject ($P < 0.001$). The relative increase average of correct movements between the two sessions was 2.7 (SD = 7.1; 95% CI [0.5;5.0]; $P < 0.001$). In 76% (32/42) of the patients an increase in the number of correct movements performed per unit of time was observed during the experimental session (Figures 2B and 2C).

Secondary end-points. Tables 2 and 3 summarize the differences between groups on the additional efficacy outcomes and all the safety outcomes. For the paretic side the total number of movements performed (correct plus incorrect) was significantly higher under vibratory feedback (average within subject difference 4.7 correct movements/min; SD = 1.1; $P < 0.001$). The average range of motion of correct movements was similar in both sessions (Table 2) with no significant statistical difference ($P = 0.13$), the same occurred with the number of pauses per minute and per correct movement ($P = 0.67$). On the normal side (Table 3) there were no significant differences on the total number of movements performed between the sessions ($P = 0.16$) and the amplitude of correct movements was similar in the two sessions ($P = 0.52$). On

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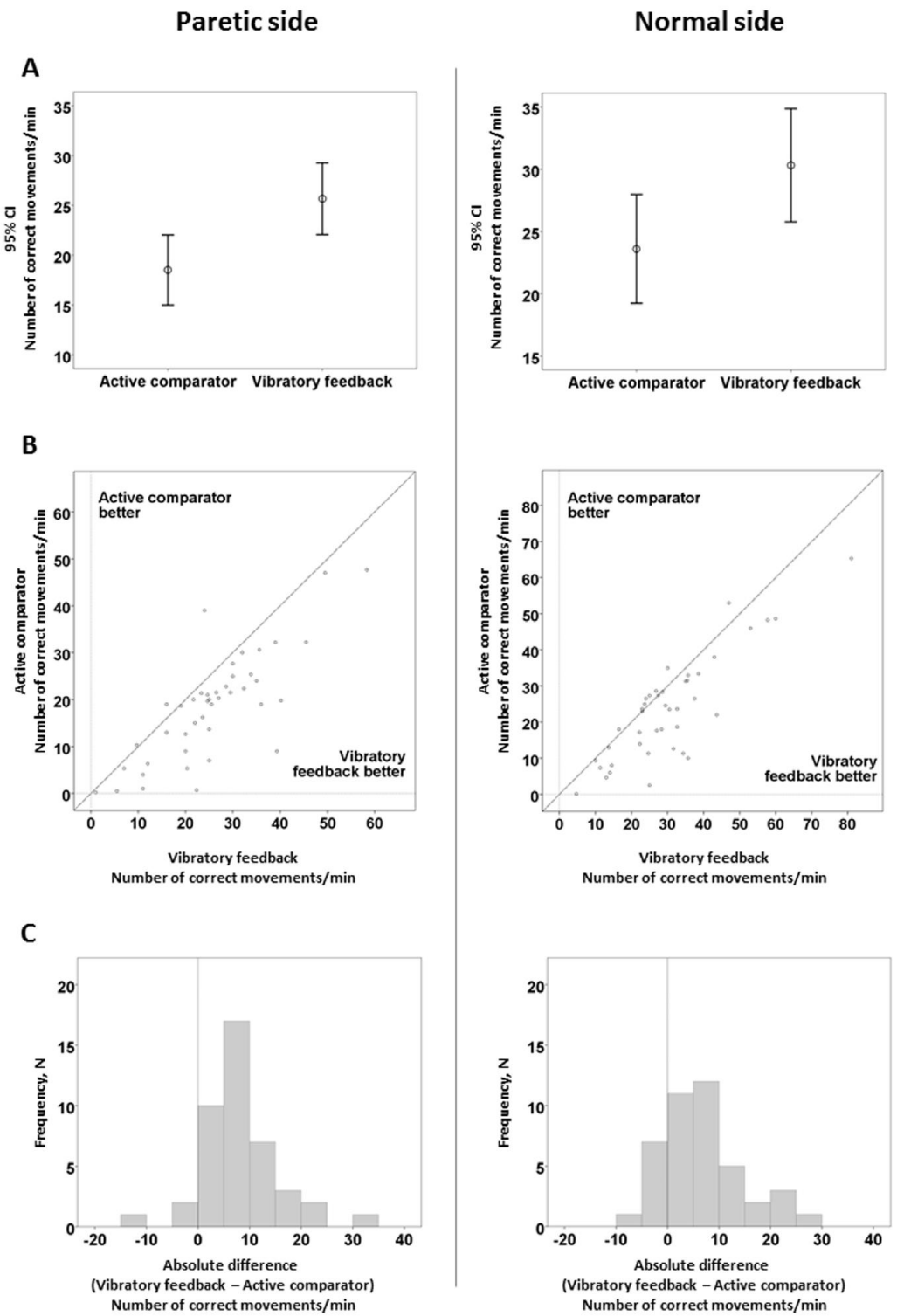

Figure 2 | Primary end point analysis in the paretic and normal sides. Figure 2A – Comparison of the 95% CI of the number of correct movements/min in the active comparator and vibratory feedback sessions. Figure 2B – Dot plot reporting paired data of the number of correct movements/min in the active comparator and vibratory feedback sessions. Difference between sessions is perceived by comparing the points to the diagonal "line of unity". Figure 2C – Histogram of the absolute differences in the number of correct movements/min (Vibratory feedback – active comparator). The dashed vertical line indicates no change.

Table 2 | Secondary end point in the paretic side

	Active comparator	Vibratory feedback	*P* value
Total number of movements per minute (correct and incorrect)	24.7 (11.6)	30.0 (12.0)	<0.001†
average (SD)	[21.1;28.8]	[26.1;33.4]	
Range of motion of all correct movements	58.4 (20.4)	55.4 (17.5)	0.13†
degrees, average (SD)	[52.1;65.5]	[50.2;62.1]	
Time between correct movements	3.7 (2.3)	3.4 (3.6)	0.34†
seconds, average (SD)	[2.9;4.5]	[2.1;4.5]	
Cumulative amplitude of correct movements per minute	1028.0 (736.3)	1258.5 (755.4)	0.001†
degrees, average (SD)	[838.1;1293.8]	[1061.2;1567.2]	
Cumulative amplitude of all movements performed per minute	1325.6 (756.5)	1494.8 (829.9)	0.003†
degrees, average (SD)	[1076.5;1532.2]	[1253.6;1766.4]	
Pauses per minute and per correct movement	0.092 (0.06)	0.088 (0.06)	0.67†
average (SD)	[0.074;0.11]	[0.071;0.11]	
Fatigue (%)*			
0 (0–5)	0	0	
1 (6–11)	97.7	74.4	
2 (12–13)	2.3	25.6	0.002‡
3 (14–15)	0	0	
4 (16–20)	0	0	
Pain (%)			
0 (no pain)	100	100	NA
1	0	0	
2	0	0	
3	0	0	
4 (interruption due to pain)	0	0	
Any adverse event	0	0	NA
Perceived quality of movement (%)			
0 (very bad)	0	0	
1 (bad)	9.3	9.3	0.08‡
2 (good)	79.1	67.4	
3 (very good)	11.6	23.3	

*Number between brackets represent the correspondence with Borg's perceived exertion scale;
†Paired samples T test,
‡McNemar's test.

both sides, the range of motion of all correct movements was approximately the double of what was set as the minimum for considering the movement correct.

None of the participants experienced a serious adverse event or other type of distress symptom during the experimental sessions or the 24 h thereafter (Tables 2 and 3). There was also no report of exertion fatigue (Borg score > 13) or pain during any of the sessions although significantly more patients reported the experimental session as moderate intensity activity (Borg's scale 12–13; 25.6% on the paretic side and 19% on the normal side). The perceived quality of movement reported by the patients after each session showed no differences between the active comparator and the experimental conditions. On the normal side, the quality of movement was given higher performance scores (Table 3). There was no correlation between the number of correct movements identified by the device and the perceived quality of movement reported by the patient on either the normal or the paretic side.

Effect of session order on the primary endpoint. Since this was a cross-over trial the possibility of a carry-over effect attributable to a short wash out period was investigated. For the paretic side, the number of correct movements was higher in the experimental than in the comparator session in the two study arms with different order of sessions. The average within subject increase in the comparator - experimental study arm was 6.9 correct movements/min (SD = 8.0: 95% CI [3.4;10.4]; P = 0.001) and in the experimental – active comparator arm 7.4 correct movements/min (SD = 6.9; 95% CI [4.3;10.5]; P < 0.001). There were no significant differences when comparing the absolute increase of correct movements per minute between the two study arms (P = 0.82). A similar pattern was found in the normal side trial. The average within subject increase in the active comparator - experimental study arm was 8.2 correct movements/min (SD = 8.8; 95% CI [4.2;12.2]; P < 0.001) and in the experimental – active comparator arm 5.1 correct movements/min (SD = 6.5; 95% CI [2.2;8.1]; P = 0.02). There were no significant differences when comparing the absolute increase of correct movements per minute between the two study arms (P = 0.21). Performing a comparative analysis of the number of correct movements per minute between the 1st and 2nd sessions, disregarding of the session type, revealed no significant differences in the paretic side (average within subject difference 0.1 correct movements/min; SD = 10.3; P = 0.95) nor in the normal side (average within subject difference -1.5 correct movements/min; SD = 10.2; P = 0.34).

Exploratory analysis of the effects of neglect, motor function and other factors on the primary endpoint. In patients with neglect the average within subject increase in the number of correct movements was 6.0 correct movements/min (SD = 4.2) on the paretic side. This increase was not significantly different (P = 0.45) from the increase observed in patients without neglect (within subject average of 7.5 correct movements/min, SD = 8.1). Regarding the trial in the normal side, the increase in the number of correct movements in patients with neglect also did not differ significantly from patients without neglect (6.0 correct movements/min (SD = 4.3) and 7.5 correct movements/min (SD = 8.1 respectively; P = 0.59).

Although there was a positive univariate correlation between the number of correct movements in the paretic side in the active comparator session and the results of the NIHSS (P = 0.004), motor NIHSS (P = 0.006), NIHSS at admission (P = 0.004) and motor NIHSS at admission (P = 0.004), none of these factors had a significant effect in the variation of correct movements per minute between

Table 3 | Secondary end point in the normal side

	Active comparator	Vibratory feedback	*P* value
Total number of movements (correct and incorrect) *average (SD)*	30.1 (15.4) [25.3;35.5]	32.61 (12.5) [28.6;36.7]	0.160†
Range of motion of all correct movements *degrees, average (SD)*	65.6 (13.4) [62.0;71.3]	66.9 (17.8) [61.8;74.1]	0.502†
Time between correct movements *seconds, average (SD)*	3.8 (4.3) [2.5;5.2]	2.4 (1.3) [2.0;2.8]	0.31†
Cumulative amplitude of correct movements per minute *degrees, average (SD)*	1460.4 (829.3) [1201.1;1798.0]	1838.8 (889.1) [1602.2;2212.8]	<0.001†
Cumulative amplitude of all movements performed per minute *degrees, average (SD)*	1726.2 (756.4) [1479.2;2035.3]	2032.4 (880.1) [1741.7;2372.0]	<0.001†
Pauses per minute and per correct movement *average (SD)*	0.093 (0.051) [0.08;0.11]	0.087 (0.054) [0.07;0.10]	0.50†
Fatigue (%)*			
0 (0–5)	0	0	
1 (6–11)	95.5	81.1	
2 (12–13)	2.3	19.0	0.039‡
3 (14–15)	0	0	
4 (16–20)	0	0	
Pain (%)			
0 (no pain)	93.0	93.0	
1	7.0	7.0	
2	0	0	1.00‡
3	0	0	
4 (interruption due to pain)	0	0	
Any adverse event	0	0	NA
Perceived quality of movement (%)			
0 (very bad)	0	0	
1 (bad)	0	0	0.727‡
2 (good)	32.6	28.6	
3 (very good)	67.4	71.4	

*Number between brackets represent the correspondence with Borg's perceived exertion scale;
†Paired samples T test,
‡McNemar's test.

sessions (P = 0.88; P = 0.93; P = 0.96 and P = 0.98 respectively.) The variation of the primary endpoint between the sessions was also not affected by gender (P = 0.60), age (P = 0.96), educational attainment (P = 0.64) or time since stroke onset (P = 0.25).

Discussion

This study explored the effect of an innovative wearable rehabilitation device (SWORD) on the quality of performance of a specific repetitive upper-limb task. The hand-to-mouth task, extensively prescribed to stroke patients in the course of their rehabilitation programs[3,27], is necessary for the completion of several important daily living activities and part of several widely used scales that evaluate upper-limb motor functioning[28,29]. To our knowledge this cross-over trial was the first to systematically address the effect of targeted vibratory feedback on the modulation of motor performance in the first month after stroke.

The performance in a training session under vibratory feedback was compared with an active comparator session (repetitive task only) within the same subject and under 3D movement characterization. The experimental setting chosen, reproduced a first post-stroke repetitive task session prescribed by a therapist before patient discharge from the stroke unit. For the efficacy outcome (primary end point) this study revealed a 2.8 times increase (95% CI [1.2; 4.4]) in the number of correct hand-to-mouth movements performed per minute of training under vibratory feedback. This corresponded to an absolute increase of 7.2 (95% CI [4.9;9.4]) correct movements per minute. The effect on the quality of the task occurred during a first session on the paretic side, without previous exposure to therapist supervised practice. Additionally, under these particular circumstances and namely within the first month poststroke, vibratory feedback was found safe (no adverse events, exertion fatigue or pain), which is in line with previous results[25].

Most importantly, for the primary outcome defined, the size of the study was appropriate and there was no evidence of a carry-over effect on the primary outcome results. No differences were detected between the results of the first and second sessions in each patient, either for the vibratory feedback or active comparator. Additionally, there was no correlation between the number of correct movements identified by the device and the patient' scores of perceived quality of movement. Although it is impossible to blind patients to a proprioceptive stimulus like vibratory feedback, the absence of correlation above reinforces the real nature of the effect measured on the primary outcome. One fifth of the patients were identified as having some kind of neglect, but there was no significant difference on the effect size attributable to this variable. The same happened for total NIHSS, motor NIHSS, age, gender education or time since stroke onset.

One interesting finding was that although the total number of movements (correct and incorrect) was also higher under vibratory feedback, the absolute effect of the vibratory feedback on the number of total movements was smaller than the effect on the number of correct movements (average within subject increase of 4.7 movements/min *vs* 7.2 correct movements/min). The analysis of the probability of correct movements among total attempts performed per minute under each condition depicted a probability of performing an incorrect movement of 1 : 3 in the active comparator *vs* 1 : 9 under vibratory feedback. This difference in the overall quality accrued with the difference in intensity observed under vibratory feedback. If we hypothesize the long-term use of the SWORD device in an outpatient setting[24], these two effects may be relevant for functional network reorganization, adaptation, motor relearning and skill acquisi-

tion[8,30,31]. Their combination may assist the implementation of early poststroke home-based regimens consisting of progressive daily repetitive skills practice while simultaneously reducing error repetition through uninterrupted training programs[7,27,31].

Other efficacy secondary outcomes such as range of motion, time between movements and cumulative amplitudes were in line with the findings discussed above. The number of pauses reflected the regularity of the physical effort performed during training and no differences were observed between the experimental and active comparator sessions, in spite of the significant increase in the overall number of correct movements in the experimental session.

The data of the trial performed on the non-paretic side of stroke patients, despite depicting similar results for the absolute and relative differences on outcomes between the two conditions, must be judged with caution. The experiment was conducted first on the non-paretic side, primarily to ensure that all participants understood the dynamic of the trial, and for this reason were more susceptible to learning effects in spite of the wash out period. Furthermore, the tasks prescribed for the non-paretic side, although of greater amplitude, were easier to complete if the overall upper-limb functioning of both sides (paretic and non-paretic) was taken into consideration. These limitations also apply for comparisons between paretic and non-paretic side effects.

Although this study strongly suggests that the vibratory feedback with 3D quantification of movement improves the intensity and quality of training, the long-term clinical impact of its use in post-stroke motor rehabilitation is not yet determined. To demonstrate generalization and clinical relevance, longer clinical trials with functional outcomes are required to assess the effect of the continuous use of this method in a parallel group randomized trial (e.g. regular treatment plus up to 30 min/day of several progressive tasks, under vibratory feedback/3D quantification, over 4 weeks). Nevertheless, the distribution of age, gender and level of education of the participants was similar to the characteristics of those patients admitted with a medial cerebral artery infarct in a stroke unit. Ischemic stroke patients with TACI, NIHSS scores > 10, mRS > 4 and Barthel index below 40 are underrepresented in the trial due to the exclusion of patients with severe aphasia or complete upper-limb plegia in the first month poststroke. Posterior circulation and hemorrhagic strokes were excluded. Patients with clinically detectable forms of apraxia were also excluded from this trial and may represent a subgroup amenable to this type of intervention[32].

Other limitations of this study deserve comment here. The duration of each hand-to-mouth session was short, 2.87 min on average. This occurred mainly due to the decision to keep the effort of the session below the maximum level of exercise tolerated by the patient and to the poor cardiovascular condition perceived by the clinician during baseline medical assessment. Pre-morbid deconditioning due to sedentary behavior has been recognized as an important problem to address in current neurorehabilitation programs[33,34]. Clinical application and long-term outpatient trials will implicate a comprehensive approach, with more tasks available for prescription and focused on progressive upper limb and lower limb training. Moreover, despite the selective inclusion criteria, the patients enrolled convey high heterogeneity with one third having subcortical lesions and the other two thirds a varied combination of cortical and subcortical lesions. Subclinical forms of apraxia were not actively searched and may have an effect on the results of the intervention[32]. All these issues must be addressed in the future planning of research and sample size estimations for the study of the mechanisms behind the effects verified[35–37].

In the field of poststroke rehabilitation, the findings of this study are in line with the well-recognized need to further characterize the interaction between training and brain plasticity in the first three months after stroke[31,35]. More specifically, having shown that a wearable device combining 3D motion analysis with targeted vibratory feedback (SWORD) was able to increase the quality and intensity of a specific repetitive task, we may now explore its long-term effects and combination with other neurorehabilitation methods in the most sensitive period after stroke. The study of the combination of error-based and reward-based training methodologies and of the effect of kinematic controlled progressive tasks on the reduction of unlearning and motor forgetting between rehabilitation sessions[36,37] is essential for the development of successful neurorehabilitation strategies that lead to improved recovery of function through reacquisition of normal movement patterns[31,38]. Finally, ongoing efforts to improve the SWORD device for home-based remotely supervised training will also address the growing need for technological tools that open the possibility for large scale cost-effective home-based rehabilitation activities[39]. These will be important in the near future to guarantee organization of services and the continuum of post-stroke care[14,15].

In conclusion, vibratory feedback was able to increase the intensity of movement and simultaneously its overall quality. If we consider that contemporary rehabilitation strategies to improve motor function after stroke are centered on high-intensity repetition of progressive skilled tasks[3,27] these findings may be of considerable relevance for future research in the field. Furthermore, the combination of intensity, over long periods of time, with quality control and motivation provided by feedback on performance are essential to modulate brain neuroplastic properties[8,27,31] and to achieve and maintain good functional outcomes.

Methods

Study design. The study was a two-sequence, two-period, cross-over study, randomized between experiment-active comparator or active comparator-experiment (1 : 1), non-blind, conducted at a single center in hemiparetic patients having their first stroke within 4 weeks before enrollment. The study was designed to evaluate the efficacy and safety of vibratory feedback, delivered through the SWORD device, and to determine if it improves the quality of movement (number of correct) on a repetitive task session performed with the upper extremity (hand-to-mouth). Both sides, normal and paretic, were tested. This study was registered at http://clinicaltrials.gov. under the Unique identifier: NCT01967290.

Participants. The study was conducted in a stroke-unit setting that provides care to 400.000 inhabitants and is based in a Portuguese tertiary hospital institution with clinical and research obligations. Patients over 18 years of age, previously independent, with a mRS 0–1[40] and admitted for a first-time ischemic stroke were screened for study eligibility between May and October 2013 (Figure 3). Participants were included if they had: 1) clinical symptoms and signs and CT or MRI findings compatible with a lesion in the territory of the medial cerebral artery; 2) persistent motor deficit on the upper limb but not plegia with a score between 0 and 2 on items 5a or 5b of the NIHSS[41]; 3) no more than 4 weeks after stroke onset; and 4) the ability to sit for more than one hour comfortably and perform two-step commands. Subjects were excluded if they had: 1) no detectable motor deficits at baseline assessment by the neurologist; 2) severe aphasia; 3) clinical dementia or mini mental state examination (MMSE)[42] below cutoff; 4) other cognitive or psychiatric comorbidity that impaired communication or compliance with the tasks; 5) severe respiratory or cardiac condition incompatible with more than one minute of continuous mild exercise in a sitting position (e.g. combing hair, brushing teeth); 6) pain or deformity that limited upper limb movement either on the normal or affected side.

Ethical issues. All participants and caregivers were provided with information about the purpose and procedures of the study and gave written informed consent. Approval from the accompanying stroke physician was also obtained to guarantee safety and management of expectations after the trial. The study received a favorable opinion by the hospital ethics committee and by the Portuguese National Data Protection Commission and the methods were conducted in accordance with the approved guidelines.

Baseline measures. Participant characterization included demographics, handedness, antecedent and comorbid conditions, pre-morbid mRS, standard medical and thorough neurological examinations including clinical aphasia, neglect and apraxia assessment, MMSE, stroke characteristics and treatments. Stroke description included: date of onset, type, location, Trial of org 10172 in acute stroke treatment classification (TOAST)[43] for etiology, admission NIHSS score and OCSP classification[44] as measures of severity and prognosis. The NIHSS score, the modified Asworth scale score[45] for muscular tonus, the Barthel index[46] and the mRS score for disability and activities of daily living were all used to create a comprehensive motor and functional profile at the time of intervention. All data were collected by a certified stroke neurologist.

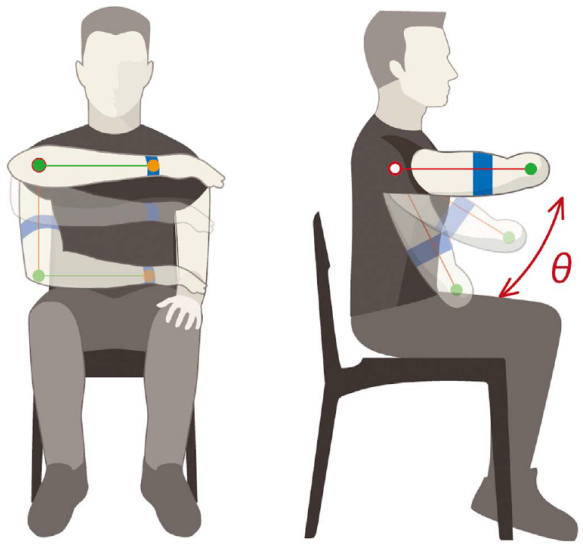

Figure 3 | Representation of the task performed. θ is the angle assessed to classify the movements as correct or incorrect. Original drawing performed by the authors V.T.C. and V.B.

Interventions. *Experimental - hand-to-mouth task with vibratory feedback.* The session occurred under vibratory feedback and 3D movement analysis. The SWORD device was in place over the patient's arm, performing continuous 3D movement analysis and providing vibratory feedback according to quality performance settings established by the clinician after patient assessment. If movement was of lower amplitude or slower than prescribed, a vibratory stimulus was delivered on the patient's wrist (Figure 3).

Active comparator - hand-to-mouth task without vibratory feedback. The setting was the same for the experimental session with the exception of vibratory feedback. The SWORD device was in place over the patient's arm, performing continuous 3D movement analysis.

Technical system used. The version of the SWORD device developed for this trial included two basic modules, one dedicated to 3D movement quantification and analysis (placed at the arm) and the other to direct vibratory feedback (placed at the wrist), connected via Bluetooth with each other and with a laptop computer[24,25]. The motion quantification module was composed by a three-axis gyroscope, three-axis accelerometer and a three-axis magnetometer. These were assembled in a wearable device that provided continuous 3D vectorial kinematics of the upper-limb and real-time analysis of the quality of movement[26]. Quality was assessed according to a biomechanical model of the upper limb and by confrontation with the parameters (range of motion, baseline position, rhythm of execution and task duration) set by the clinician for the hand-to-mouth task (Figure 3)[26]. The vibratory feedback module included two DC motors, with eccentric masses encapsulated in a cylinder 25 mm long and 8.8 mm in diameter[47], and was programed to deliver vibratory stimuli at a frequency of 200 Hz and an amplitude of 46 m/s2 at a rated voltage of 2.6 V[25]. The vibratory feedback was set to trigger every time that the patient did not perform a correct movement, either because the maximum amplitude was not achieved, the baseline was not reassumed after a correct movement in amplitude or the movements were occurring at a slower rate than prescribed. Once triggered, the vibratory stimulus was continuous until a correct movement was performed[25].

Randomization. Eligible participants were randomly allocated in a 1 : 1 ratio to two study arms. Balance between arms was guaranteed using random permuted blocks of two. For one arm the order was an experimental session followed by the active comparator session, for the other it was the reverse. Although motor deficits after stroke are not expected to change significantly within the same day, either spontaneously or due to the intervention, the randomization of the session order was performed to avoid carry-over effects due to fatigue or learning. Based on previous experiments[25] an obligatory washout period equal to 20 minutes plus the double the duration of each session was set.

Blinding. Although the investigators and participants were aware of the vibratory stimuli, they were blind to the primary and secondary movement outcomes being measured, as those were automatically recorded by the device and only available at the end of the trial. The statistical analysis was performed blinded for experimental or active comparator status.

Primary outcome definition. The primary outcome with respect to efficacy was the number of correct movements performed per minute within the duration of each hand-to-mouth session, a measure of the quality of movement. This measurement was independent of the investigator and assessed automatically by the device as described elsewhere[48].

Secondary outcomes definition. Additional efficacy outcomes were considered: i) the total number of correct and incorrect movements; ii) the average range of motion in degrees (correct movements); iii) the average time between correct movements in seconds; iv) the cumulative amplitude of correct movements in degrees; v) the cumulative amplitude of all movements (correct and incorrect) performed in degrees; and vi) the number of pauses identified, defined as interruptions exceeding the average time between correct movements plus one standard deviation. The SWORD device assessed all these measures automatically.

For the purpose of assessing safety the following outcomes were used: i) patient expresses feeling fatigued using a visual analogical scale adapted from Borg's perceived exertion scale[49]; ii) patient expresses feeling pain using a visual analogic scale; iii) other distresses identified by the patient or detected through monitoring, at the end of the session and 24 h thereafter; and iv) self-perception of overall quality of movement performed during each session. The need to use adapted visual analogue scales for these safety outcomes (i, ii and iv) resulted from the population's low education.

Sample size estimate. In a pilot study (Bento VF, PhD thesis, 2012), the number of correct movements in the active comparator was estimated at 12.4 per minute (SD = 6.9). Considering a power of 85% and a two-sided 0.05 significance level, 38 patients would be necessary to detect a difference of 60% in the number of correct movements per minute between the active comparator and the experimental sessions for each subject.

Statistical analysis. To assess between-group differences in clinical and demographic variables of the patients allocated to the two study arms, independent samples T test, Mann–Whitney U test, qui-squared test and Fisher exact test were used. To compare the primary and secondary outcomes between the experimental and active comparator sessions on the patient's same side, paired samples T test and McNemar's test were used. To identify possible carry-over effects attributable to the cross-over design two parameters were separately analyzed for the paretic and normal side: i) the differences in the absolute variation of the primary outcome among the two study arms, using independent samples T test; and ii) the differences in the number of correct movements per minute between the first and second sessions, regardless of session type, using related samples T test. To identify possible determinants of the base-line performance and of the improvement in motor outcomes observed during the experimental session, additional analyses were performed using simple and multiple linear regression models. The statistical analysis was performed in SPSS 21.0 considering a two-sided 0.05 significance level.

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Author contributions

Study concept and design: V.T.C., V.B., C.B. and P.C. Acquisition of data: V.T.C., D.D.R., M.C., L.R., L.F., R.B., C.M., A.A. and C.B. Analysis and interpretation of data: V.T.C., L.R., V.B., B.C., C.B., N.P.R. and P.C. Critical revision of the manuscript for important intellectual content: All authors. Obtained funding: V.T.C., V.B. and P.C. Administrative, technical and material support: V.T.C., D.D.R., L.F., R.B., C.M., L.R., M.C., A.A., C.B. and V.T.C. Study supervision: V.T.C., V.B., M.C., V.T.C., C.B., N.P.R. and P.C.

Additional information

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Part III - Discussion and conclusions

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3. Conclusions

1. Achievements

This section is dedicated to the integrated discussion of the impact of the major accomplishments along both research pathways pursued: cognitive training with COGWEB and motor training with SWORD. The specific achievements that resulted from the research processes described within each set of original studies (articles I – III and articles IV – VI) are now discussed together as a continuum, in articulation with the research questions presented beforehand and the global vision for this work. Redundancy with the contents of the articles was avoided. Therefore, most of the aspects concerning specific limitations and comparisons with other strategies, technologies and systems, are better addressed within each article.

This analysis focuses on the research questions put forward for this thesis and follows three main perspectives: clinical, technological and organizational. Research questions 1 and 3 are mainly approached in the clinical subsection, while question 2 is mostly related with organizational issues. All questions are concerned with technology and its impact on health care.

a) Clinical

From a clinical and neurophysiological point of view, both cognitive and motor training share the same principles. This relationship starts in the central nervous system, at a cellular and molecular level, where motor and cognitive functions are supported by similar brain plasticity mechanisms[6,54,59]. They are organized over several different anatomic locations in the brain, with specific eloquent cortical areas but supported on neuronal circuits with significant cross-modality overlap[225] and economy of connectivity[226]. Furthermore, neurobiological properties which are transversal to major brain functions, like learning, development and response to injury, degeneration and pharmacological and nonpharmacological interventions follow very similar patterns[6,54,57,59].

The work described in this thesis was organized into two research pathways dedicated to the development and validation of two different technological e-health solutions. Although they stem from different perspectives from a technological point of view, in a clinical context they are very similar. At their starting point, both strategies share the same neurophysiological principles, namely the current perception of the plastic properties of

brain tissue[6,54,57,59]. As they evolved, through step-by-step clinical validation, one of the most striking aspects was a growing trend towards convergence and overlapping. In fact, a strong perception was built, that clinical applications of systems like COGWEB and SWORD, as they come closer to real life scenarios[227], will necessarily be combined[228]. Most neurologic and psychiatric patients are increasingly recognized as having cognitive and motor deficits and neurorehabilitation programs are becoming like large scale orchestras, where several interventions must be organized together in specific time frames and intensities[227,229,230]. Working tools designed to allow prescription of tasks and continuous monitoring of their execution, either remotely or in the presence of an experienced professional will be of great usefullness in such settings[6,25,177,231-233]. Considering the research questions proposed, and from a clinical point of view, the work in this thesis allowed the confirmation of several important points. Questions 1 and 3 relate to each of the pathways, and had a common structure, subsequently itemized according to the specificities of cognitive and motor training, the stage of clinical use and validation, and the level of maturation of each technological tool.

It was possible to develop two novel information systems dedicated to cognitive training and to motor training. With the previously defined concept model in mind, both systems were assembled following a patient- and professional-centered approach. Articles I and II described the development and characteristics of the COGWEB system and initial usability data. One of the most important findings was related with the usability of the system. In article I it was shown that patients with a wide spectrum of ages and years of formal education were able to use the system. The majority of the patients managed to learn it from the first session, while 39% required some type of coaching from a relative or their therapist. The ease of use with which patients interacted with the system was further explored and proved to be important during the extended usability tests described in article II. This study demonstrated that patients adhered to cognitive training and were willing to commit to high intensities of cognitive training (average of six hours per week) over long periods of time (82.8% of patients compliant at six months). The findings took on greater significance since they were observed across several important groups of pathologies such as neurodegenerative diseases, static brain lesions, subjective memory complaints and depression. All have a high incidence and prevalence in the population, with varying degrees of associated impairment. Another aspect which was of clinical relevance was the

preliminary finding that the combination of web-based cognitive training activities with regular face-to-face meetings with a therapist could translate into a two hour increase in training per week.

These results of adherence and intensity provided us with essential data for further research planning[234,235]. It is now possible to anticipate the level of exposure to training or cognitive interventions over longer periods of time using the COGWEB system. This is crucial to explore the biological significance of such doses of cognitive intervention in randomized trials and other types of clinical studies aimed at studying the impact of cognitive training in several disease models and stages of diseases or even prevention strategies[6,133,236-239]. Some of these studies are already ongoing, as is the case in the fields of multiple sclerosis (NCT02193906, https://clinicaltrials.gov/), schizophrenia or long term cognitive monitoring, but they are not the subject of this particular thesis[240,241].

For the SWORD system, the most significant achievement, from a clinical point of view, was described in article VI, which dealt with a randomized clinical trial using a device previously described in articles IV and V. The trial explored the effect of the SWORD system on the modulation of a standard motor training task frequently used in rehabilitation plans of stroke patients. It was demonstrated that the SWORD system was able to improve the quality of motor task performance, namely by reducing the probability of performing an error during a motor training task, from 1:3 to 1:9. This strategy may be useful to improve the efficacy of training on motor relearning processes after stroke and will be further studied in the near future[47,48,50,242].

The tolerability of the vibratory stimuli used in a stroke rehabilitation context was also an important finding of articles IV and VI. Vibratory stimuli were found to be safe, even over longer exposures, and the type of vibratory feedback used during the clinical trial was not associated with clinically relevant fatigue, pain or distress.

The study described in article V, although essentially technological, from a clinical point of view, opens the possibility for automatic evaluation of motor performance and development of more efficient and objective tools for monitoring of patients over time. These can be of great usefulness in clinical trials with motor and functional outcomes and in clinical decision making during long term rehabilitation programs[52,243,244]. This

development was crucial for the success of the clinical trial described in article VI. Further clinical studies are being planned to explore the diagnostic and monitoring applications of the SWORD system.

The work developed so far has allowed us to obtain a clearer understanding of several important characteristics of training which are being useful for planning further development and research activities. Putting both processes into perspective, it may be said that they were built around a triad composed of tasks, repetition and gaming. For each brain function in which we wanted to intervene a series of very specific tasks were constructed and a system was assembled that allowed their prescription and an accurate control of exposure by an experienced professional. The process of repetition and training was guaranteed by using several degrees of immediate feedback and gamification strategies, with the objective of trying to increase motivation while avoiding deleterious effects of frustration or excessive competition[245,246]. Despite these similarities between both systems, there are some important clinical differences that are worth addressing here. Cognitive training is concerned with several important and diverse brain functions (e.g., attention, executive functioning, memory, language, orientation, constructional ability and processing speed) which overlap or interfere with each other in certain aspects, and have the possibility of creating a significant impact on daily life. At the same time, motor training is concerned with a single important function, namely movement of the whole musculoskeletal system of our body, as well as several aspects within it, such as strength, coordination, tonus and velocity of execution. Although it is possible to develop tasks to train these functions, with scenarios which to a greater or lesser extent emulate daily living activities, the control of execution of the tasks is very different. With the advent of computers and their closer proximity to human cognition processes, it has become quite easy to verify the answers to cognitive tasks and control the training process. However, for each motor task, we have to develop hardware which is able to collect real time information, decompose all aspects of movement and orient training in a way which is as close to the role of a therapist as possible. Furthermore, the issue of tolerability and the impact of gamification strategies may have very different clinical consequences. In cognitive training, fatigue is a phenomenon that is predominantly dependent on neuronal processes and the human brain[6,247]. In adults in particular, it has very robust mechanisms that reduce motivation and prevent damage from excessive training[248]. However this may

not be true in some psychiatric disorders, in the period shortly after an injury or during developmental phases[6,247-249]. In motor training, fatigue is the result of a combination of brain, musculoskeletal and cardiovascular processes with all the implications and adverse effects associated with them[250,251]. These differences have repercussions on the relevant aspects to induce or avoid during training processes and consequently practical implications on the design of the motivational features (e.g., goal setting, feedback and gaming scenarios) used in each system.

The differences experienced directly during cognitive and motor training with patients, coupled with the stage of knowledge and clinical practice within each field, explain the different stages of maturity of COGWEB and SWORD, with the former being used as a clinical tool that replicated current cognitive intervention strategies, while the latter was used only to prescribe and control a single task in a very controlled clinical trial.

b) Technological

All the research questions approached throughout this study were built upon the premise of guaranteeing a continuous flow of technological development. This was necessary for the construction of two robust clinical and research tools in the field of cognitive and motor training. The success of most of the scientific studies planned was dependent on these technological achievements. Simultaneously, the scientific processes contributed the most valuable feedback for their consolidation.

Two information systems were consolidated, COGWEB, aimed at cognitive training, and SWORD, dedicated to motor training. They were developed following the premises laid down in the sections on the concept model and vision and their most important characteristics are described in articles I through VI and in the documentation that supports their intellectual property rights[252-255].

At this point, the level of maturation of each of these systems may be best described by their technology readiness levels (TRL)[256], a measure originally developed by the National Aeronautics and Space Administration (NASA) and perfected by the United States Department of Defence (USDoD) and used to assess the maturity of evolving technologies, as they progress from conception to application[256,257]. Applying this metric, COGWEB is in a TRL 9 phase where the current system with 45 fully developed serious games for cognitive training has been “flight proven through successful mission operations”, as

described in articles II and III. In comparison, the SWORD system is probably ranked as a TRL 6 or 7. A system prototype was demonstrated in a relevant environment (article VI). Since the system was conceived to incorporate several rehabilitation tasks and to be used at home, and only one task was tested in a stroke unit based trial, this corresponds better to a TRL 6.

Both technologies developed have the potential to improve patient access to these types of therapies in current health systems and this issue has been explored with COGWEB. In article III, it was shown that during the implementation of the COGWEB network, more than 45 centers and 300 new patients in Portugal and Brazil started to use the COGWEB system. Currently, 5 new patients per day on average start using this system in their cognitive intervention plans. Although it is an indirect measure of impact, these numbers highlight the systemic effects of the use of these systems on a wider scale, integrated in national health systems.

Most relevant, in their mature state, both the COGWEB and SWORD systems may be better defined as applied research tools in the field of clinical neurosciences. They will allow the implementation of evaluation studies of diverse training strategies, either alone or combined with other interventions like pharmacological, stem cell, non-invasive or invasive brain stimulation therapies[258-261]. In this respect the network functioning of both systems will respond to the growing demand for faster multicenter clinical trials, and will also facilitate the process of clinical utilization of the knowledge produced within research networks. This may contribute to faster improvements in the quality of care and at the same time to the sustainability of modern health systems. These issues are currently largely debated in translational research forums[221,262].

c) Organizational

The scientific and technological work carried out in this thesis was supported by very specific research and development projects. Their implementation and execution over time resulted in several organizational accomplishments *per se*. From the beginning, both research and development pathways required the adoption of innovative methods to guarantee the sustainability of the projects, the development teams, and the collaborative networks created. Some strategic options taken along the way are noteworthy of a mention here. They proved to be a determining factor for the successful development of the

technological tools, within stipulated time frames and with the required quality, and may be crucial for long term achievements. In general, they corresponded to organizational accomplishments in response to major trends in current health systems organization of care and new funding processes of investigator-driven research projects.

Collaborative network functioning

Both systems were developed as collaborative working tools. This concept involved sharing the tool and its development process with a significant number of different professionals and diverse institutional settings. Through this process, it was possible to combine early scientific data acquisition under very controlled circumstances, with the necessary exposure, redesign and maturation of the tools (prior to wider use). In this way it was feasible to improve the final proficiency of the tools developed and to incorporate from the start, the needs described by multiple professionals specialized in very different diseases at very different institutions and settings. This aspect was critical for goals such as dissemination and integration in future health systems (translational research pathway) and contribution to the feasibility of multicenter research studies in the field of neuroscience-driven rehabilitation[221,262]. In addition, this type of functioning was also crucial for the continuous improvement of the quality of processes, adapting to changes in knowledge and institutional organization and maintaining the systems as up-to-date as possible. These aspects were best explored in the COGWEB system (article III), due to its more advanced stage of maturation. In this article, the network of centers that supports the development of the system and the studies that assess its efficacy is the same network where practice guidelines are being established and public health gains being assessed. This is in line with the most current recommendations on strategies to shorten translational research pathways[221,262] and the most recent European framework program for research and innovation (HORIZON 2020)[263-265].

Sustainability

COGWEB received a very limited funding from the Portuguese Neurological Society and public funding was part of the driving force of the SWORD project, initially through the Portuguese Science and Technology Foundation project PTDC/SAU-NEU/102075/2008. Nonetheless, the level of funding required for both projects to achieve a high level of clinical performance and complying with the current requirements for health information

technologies and medical devices implied additional long term strategies. The research and development process evolved in parallel with the incorporation of two medical technology start-ups, Neuroinova in 2011 and Endeavour Lab (Stroke of Genius) in 2013, which attracted further funding and investment. This option was crucial for the success of the initial research process although it required a significant effort and the acquisition of uncommon competencies for a clinical neurologist. It later proved its worth and was the main factor which allowed the nuclear team of clinical and technological developers to stay together since 2005. Over the last 20 years the Portuguese scientific community has been under a great deal of pressure from talent catcher markets like the United States, Europe (Germany and the United Kingdom) and even Asian countries[264]. In the near future the ecosystem established over these years of work and collaboration will provide invaluable technological, clinical, scientific, industrial and business solutions required to innovate and drive the path from ideas to dissemination, growth and finally public health gains successfully[263,264].

2. Present and future work

In spite of the results accomplished with this thesis so far, the projects that comprise it are long term paths. Organizational issues, new research questions and lines of development are already underway and deserve further comment here.

a) Consolidation of organizational and operative issues

There are two intertwined domains that will determine the capacity to achieve further accomplishments and a wider public impact of research results. These are collaborative research networks and business networks.

Networks as tools for research

As discussed in article III, collaborative networks are emerging as central tools for health research. Furthermore, they may be effective reducing the time between the production of relevant scientific knowledge and its dissemination and adoption by health professionals and institutions. These aspects are crucial if the major goal is to have an impact on public health indicators. In this regard, an important initiative is the consolidation of the COGWEB network. To achieve it, a new project was started in early 2014 called "Consolidation and development of a translational network dedicated to cognitive training in neurological diseases – COGWEB network"[266]. It aims to further expand the number and profiles of centers that use the COGWEB system in their activities, improve the transmission of knowledge within the network and improve the quality of cognitive training programs provided within the network of partners, through the implementation of quality management tools.

A similar process has started this year with centers dedicated to stroke rehabilitation. A set of pioneering institutions and professionals began to use the SWORD system in their activities while at the same time contributing with valuable insights to the development of the system and generating data on motor rehabilitation that will benefit all the partners in the network. Through this process we plan to work directly with the end users in a relevant environment from the start, developing a better tool in less time, while simultaneously preparing the field for its adoption and dissemination, if and when it is scientifically proved as useful.

Entrepreneurial backbone

Another important organizational aspect is the consolidation of the start-up companies that emerged from the professionalization of the research projects described (Neuroinova and Stroke of Genius). Much of the ongoing scientific processes and specialized human resources necessary to accomplish the tasks and milestones proposed were incorporated inside these companies. They are now the backbone of future scientific developments and much of the funding necessary will come from the commercialization of the systems developed and venture funding they are able to attract. Both companies will operate in the field of clinical neurosciences, aiming to improve people's lives and the quality of work of institutions and professionals through their products and tools. In this process, high quality technological development and scientific production will not be a goal *per se*. Working in a similar way to an assembly line, they will be their chief means to develop and implement the most targeted and innovative products in the fields of cognitive and motor rehabilitation.

b) New research pathways

At the beginning of this work, two major research and development paths were defined: a cognitive training pathway that originated COGWEB, and a motor training pathway that led to SWORD. During the development and clinical validation studies, several scientific results and observations gave origin to a reorganization of ongoing and future research activities. Currently, besides a path that continues the development and validation process of instruments aimed at neurological intervention and treatment, a completely new line has emerged, focused on the design of tools to improve or support decision making, either through monitoring or diagnosis.

Rehabilitation and treatment

In this field the aim is to continue to obtain information on the impact of cognitive or motor training interventions across several disease models. Randomized trials of cognitive training interventions using COGWEB have already been started in patients with schizophrenia[240] and multiple sclerosis (NCT02193906, https://clinicaltrials.gov/). Studies in stroke, Parkinson's disease and addiction disorders are about to start, thus bringing together several institutions and academic and research interests within the COGWEB

network. For the planning of these studies the data obtained on the adherence and intensity (article II) to online cognitive training were crucial.

Nowadays, the complexity of cognitive and motor rehabilitation programs is increasing[229]. For this reason it has become very important to obtain data on the combination of treatments and on the modulation effects they have on each other. In this respect some relevant new research questions arise. How do motor and cognitive training interact? How can the effects of cognitive and motor training be modulated by pharmacological or nonpharmacological interventions? How can cognitive and motor training be combined with other brain stimulation methods like transcranial magnetic stimulation, transcranial direct current stimulation or deep brain stimulators? How should neuroplasticity promoting methods like stem cells, growth factors or even aerobic exercise, be combined or modulated by cognitive or motor training interventions?

Another relevant domain is directly concerned with research methodologies in the field of neurorehabilitation. New strategies are needed: firstly to identify subgroups of patients with the capacity for neuroplasticity that may have a better response to interventions, and secondly to shorten the time necessary to know whether a specific pharmacological or nonpharmacological intervention has a beneficial effect on the plastic properties of the brain tissue or on the brain functioning in the most important disease models. In this respect it is important to develop research lines with the purpose of finding new surrogate biomarkers of these effects[6]. Are there strong molecular or neuroimaging (structural or functional) correlates of the effects of training that can be used to conduct a faster assessment of the potential of new strategies? Can they be used in ordinary clinical settings to improve decision making during rehabilitation programs? Can the rate of improvement in response to a certain amount of training be itself a measure of plastic brain reserve? Furthermore, when assessing the long term effects of medications or interventions on brain plasticity there is room for the incorporation of new ideas and optimization of randomized clinical trials methodology[6]. For example, a standardized home based cognitive training background could function as a more stimulating environment with a catalyst effect on brain plasticity. This could have the potential to unravel the effects of successful interventions within a shorter time-window during a randomized controlled clinical trial. This strategy resembles, to a great extent, what happens nowadays with treatment decisions

for coronary artery disease, where cardiac function is analysed in response to an exercise challenge before decision[267]. Similar "stress" strategies are used for optimizing treatment prescription in endocrine disorders (e.g., adrenocorticotropic hormone infusion test)[268], asthma (e.g., bronchial reactivity tests)[269] or motor symptom treatment in Parkinson's disease (e.g., the L-DOPA test)[270]. To sum up, either through measuring function[271], evaluating injury at baseline[243,272] or assessing plastic brain reserve in response to a specific challenge[273], it is possible to predict response to subsequent plasticity-promoting therapies or to reduce the time to evaluate a given intervention in a randomized trial[6].

Monitoring and diagnosis

Although COGWEB and SWORD were initially designed as research tools to study cognitive and motor interventions, their potential to help clinical decision making is striking. Data produced during long term monitoring of training activities and its continued analysis by specialized professionals supervising treatments has the potential to improve therapeutic decisions. If we consider the spectrum of progressive diseases and difficult differential clinical diagnoses like normal ageing *vs* dementia or cognitive impairment due to depression *vs* dementia or dating the onset of cognitive decline in relapsing remitting diseases like multiple sclerosis or schizophrenia, it is possible to find diagnostic usefulness in the different responses to training. To approach these problems, a new tool called Brain on Track was developed. The starting point was the analysis of monitoring data obtained with COGWEB over the years, and the selection of the parts of each cognitive training exercise (levels) that had the most discriminative power to detect changes in cognitive performance within each cognitive domain[241]. With this information, an assessment battery was assembled on a web-based platform and coupled with a short messaging service (SMS) that guided individuals to perform their periodic online assessment. This instrument was designed for long term monitoring of populations at risk for cognitive decline and is presently being validated in a cohort in the North of Portugal (a partnership with EPIPorto, Institute of Public Health, University of Porto)[274]. The process of further development and clinical validation of this new method is the subject of an ongoing PhD project (Luis Ruano, 2014) that will explore its clinical use in early detection of cognitive decline in diseases like multiple sclerosis[275] and how to modulate patient referencing from the community to specialized memory clinics[274].

In the field of diagnosis, taking advantage of the network functionalities of COGWEB, a new instrument designed for patient cognitive assessment was developed. It is called Computer Aided Cognitive Assessment Online (CACAO). The starting point for this tool was the perception among the professionals within the COGWEB network of the need for a more practical cognitive assessment method that could rank patients immediately after completion and provide an automatic report of results. CACAO works on a tablet PC and uses more ecological tasks that are remotely based on tasks used for assessment in classic pen and paper batteries. The scenarios, objects and design were planned to increase motivation during task execution in our population. Special attention was paid to the usability of the back office, operated by professionals, and to personal identification credentials, which are very important for use in future clinical trials. This tool is already in use at two of the COGWEB network centers with data obtained for more than 200 patients and controls. As cognitive assessment activities absorb about 80% of the time of the neuropsychologists within the COGWEB network, CACAO will be a central element in the sustainability strategy of this collaborative network, empowering the professionals with a more agile instrument dedicated to cognitive assessment.

As explored in article V, a similar approach to the field of monitoring and diagnosis is being pursued with the SWORD device, with the focus on automatic, observer-independent assessment of motor functioning. Due to the characteristics of motor training, there is a special focus on the capacity to detect and anticipate fatigue, musculoskeletal pain, spasticity and other common complications during long term motor rehabilitation programs.

3. Conclusions

The development of this thesis has allowed the reflection on some of the most important problems related with the rehabilitation of cognitive and motor deficits and how to effectively harness neuroplasticity. Considering the research questions initially proposed the following milestones have been accomplished:

1- The development of an innovative research tool for cognitive training interventions (COGWEB). It was shown to improve the intensity and quality of training while ameliorating patient access to treatment and management of specialized health resources. Usability data revealed that 95% of the patients found it useful and were motivated to use COGWEB at home, although 39% required a period of coaching before independent use.

2- The generation of objective data on the adherence and overall treatment intensity obtainable over longer periods of training in relevant disease groups in a memory clinic setting. At six months the compliance rate was 82.8% and the average training intensity was six hours per week. These data are crucial for planning cognitive interventions in clinical practice and designing future research in the field.

3- The organization of the first collaborative network dedicated to cognitive training (the COGWEB network). During its first year of functioning, 68 professionals from 41 centers adhered and 298 patients gained access to regular cognitive training activities. These dynamics will be crucial to improve the translation and dissemination of the knowledge generated within the network and to help us to create a positive impact on public health. Furthermore, similar methodologies can be applied for the dissemination of motor training strategies using the SWORD system.

4- The development of a novel portable system aimed at the improvement of motor training interventions (SWORD). This system is wearable, designed for ordinary clinical settings or home use and combines targeted vibratory stimulation with 3D motion characterization.

5- It was demonstrated that targeted vibratory stimuli were well tolerated by stroke patients and capable of improving the quality of motor task performance in a randomized trial with acute stroke patients. The number of correct movements on a hand-to-mouth task was increased by an average of 7.2/minute, while the probability of performing an error was reduced from 1:3 to 1:9.

6- It was demonstrated in an exploratory study that 3D motion analysis components of the SWORD system are able to automatically reproduce a conventional motor assessment scale like WMFT. The system reproduced the assessment results of a trained clinician in two of the tasks of the WMFT. This opens the possibility of developing automatic motor evaluation and monitoring tools aimed at improving decision-making during long motor rehabilitation programs.

Following these two lines of research was a complex yet unique endeavour, because it permitted the consolidation of unifying perspectives (clinical, technological and organizational) in the domains of neurorehabilitation and neuroplasticity. In this way, motor and cognitive functions, as well as their training, are better perceived as a continuum.

This new understanding is now the backbone of much of the current thinking and further development processes already on the way. It will possibly allow us to forge the path from scientific knowledge production to relevant applications and translate innovation into public utility. In this respect, the funding for this thesis and the entrepreneurial ecosystem which underpinned it created the same pressure and difficulties found in innovative solutions for future developments and sustainability.

As expected, there are no definitive answers or knowledge produced in such fast evolving fields as neurorehabilitation, neuroplasticity and neuroscience driven information systems. The answers provided to the research questions proposed herein, allowed the clarification of important subjects while at the same time bringing new and fascinating hypotheses for further studies and developments.

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Appendix

Applicable legislation and regulations

Decree-Law 74/2006 dated March 24, as amended by Decree-Law 107/2008 dated June 25 and Decree-Law 230/2009 dated September 14. Regulation of Studies of the University of Aveiro, regulation 214/2012, DR 2nd series, 109 dated June 5. Regulation of the Doctoral School of the University of Aveiro, order 6403/2011, DR 2nd series, 74 dated April 14. Regulation for accreditation of training and professional experience at the University of Aveiro, order 7047/2011, DR 2nd series, 89 dated May 9. Regulation of the Doctoral Programme of Health Sciences and Technologies of the University of Aveiro, order 12177/2010, DR 2nd series, 145 dated July 28, DGES R/A-Cr 38/2010, accreditation process NCE/09/00462. Regulation of the Health Sciences Department of the University of Aveiro, regulation 641/2010, DR 2nd series, 145 dated July 28.

Author contribution statement

For all the six original research studies included in this thesis (published: articles I, II, IV–VI; under review: article III), Vítor Tedim Cruz was the first (articles I–III, V–VI) or second (article IV) co-author and was responsible for: the study concept and design; obtaining funding; acquisition of data; analysis and interpretation of data; critical revision of the manuscripts for intellectual content; administrative, technical and material support and study supervision.

(article 64º, regulation 214/2012, DR, 2nd series, 109 dated June 5).

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