

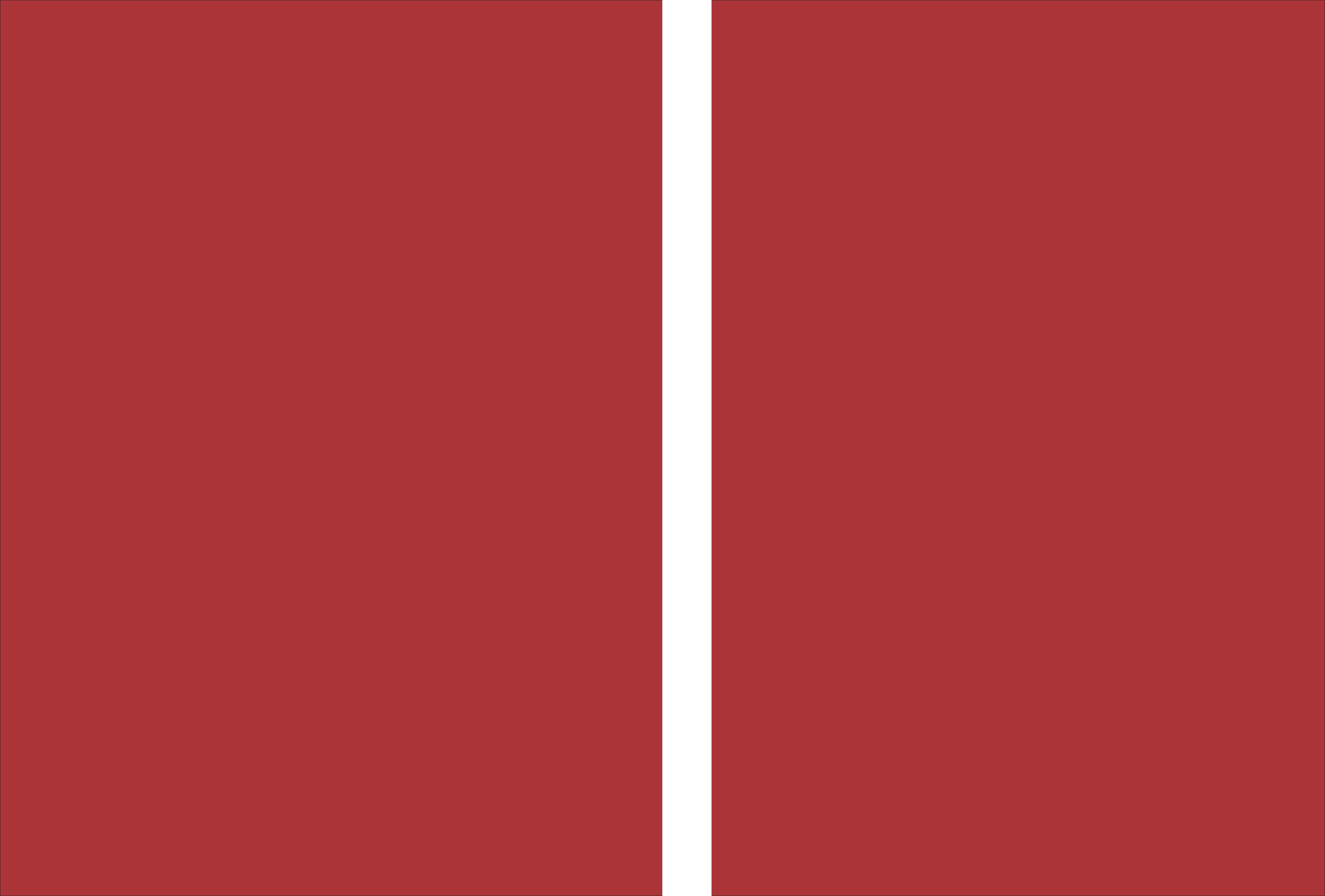


Universidade do Minho
Escola de Medicina

Raquel da Glória Teixeira de Carvalho Ribeiro **Bobath Concept and Brain-Computer Interface: combined approach to enhance neuroplasticity in chronic stroke**

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Tese de Doutoramento em Ciências da Saúde

Trabalho efetuado sob a orientação do
Professor Doutor João José Cerqueira
e do
Professor Doutor Nuno Dias

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DECLARAÇÃO

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTA TESE APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.

Universidade do Minho 12/03/2018

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DECLARAÇÃO DE INTEGRIDADE

Declaro ter atuado com integridade na elaboração da presente tese. Confirmando que em todo o trabalho conducente à sua elaboração não recorri à prática de plágio ou a qualquer forma de falsificação de resultados.

Mais declaro que tomei conhecimento integral do Código de Conduta Ética da Universidade do Minho.

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Bobath Concept and Brain-Computer Interface: combined approach to enhance neuroplasticity in chronic stroke

Abstract

One of the major goals of stroke rehabilitation is the recovery of upper limb function. Physical therapy, based on the Bobath Concept (PT), is the most common intervention in stroke patients, and shows good results, despite the lack of well-controlled trials. In addition, neurofeedback techniques using electroencephalography (EEG)-based brain computer interfaces (BCI) to guide motor imagery, have recently emerged as valuable rehabilitation tools, however, little research has been carried out in stroke patients. Studies showed that the main strategy adopted during motor imagery (MI) training involves familiar tasks, and only seemed beneficial in chronic stroke patients, specially associated with other forms of intervention, such as physical therapy. Nonetheless, it is not clear if and how MI training with neurofeedback BCI systems, promotes not only clinical but also neurophysiologic changes in stroke patients. Moreover, we found that despite the incremental use of EEG-fMRI studies, there is lack of exploration of the relationship between changes in brain symmetry index (BSI) and blood oxygen level-dependent (BOLD) responses in chronic stroke patients. The second part of this thesis aims to: analyze the relationship changes in BSI and BOLD responses during multitasks (motor execution or MI for both the affected/unaffected hand). We also assess the neural mechanisms underlying the improvement of upper limb function after PT and test whether the association of a MI with neurofeedback EEG-based BCI to a PT program can further enhance the efficacy of the latter in neuroplasticity and in the recovery of upper limb function in chronic stroke patients. We found that time post stroke was negatively correlated with contralesional cerebellum activity and changes in BOLD activation patterns were related to BSI variation and different from the affected compared to unaffected hand movement and during execution compared with MI. It seems that 4-weeks of a PT program promotes recovery of upper limb function and neuroplasticity even in chronic stroke patients, in particularly in ipsilesional precentral and post central area and contralesional cerebellum. MI training guided through real neurofeedback from BCI can help to improve upper limb function and brain symmetry compared to sham neurofeedback, in chronic stroke patients, however, conclusions must be carefully taken into consideration, given the extremely limited number of patients. In conclusion, PT can change upper limb function and neuroplasticity in chronic stroke patients, MI guided through neurofeedback from BCI can be an adjunctive treatment since improves not only upper limb function but also brain symmetry. Large trials of PT associated to MI training with BCI in this population are justified.

Conceito de Bobath e Interface Cérebro-Computador: abordagem combinada para melhorar a neuroplasticidade em doentes crónicos com acidente vascular cerebral

Resumo

A recuperação da função do membro superior é um dos maiores objetivos da reabilitação de doentes com acidente vascular cerebral (AVC). A Fisioterapia baseada no conceito de Bobath (FT) é uma das intervenções mais comuns em doentes com AVC, demonstrando bons resultados, apesar da falta de estudos bem controlados. Recentemente surgiram como ferramentas valiosas de reabilitação o uso de neurofeedback fornecido por interfaces computador-cérebro (BCI) através de eletroencefalografia (EEG) para guiar a imaginação motora (IM), no entanto, poucas pesquisas foram realizadas em doentes com AVC. Estudos de investigação demonstraram que a principal estratégia adotada na IM envolve tarefas familiares, parecendo benéfica apenas em doentes crónicos em associação a outras formas de intervenção, tais como a fisioterapia. No entanto não é claro, se e quando o treino de IM guiado por o neurofeedback de um BCI promove não só alterações clínicas mas também neurofisiológicas. Além disso, descobrimos que apesar do aumento de estudos com EEG-fMRI, há falta de exploração da relação entre as mudanças no índice de simetria cerebral (BSI) e as respostas BOLD (*Blood Oxygen Level-Dependent*) em doentes com AVC crónicos. A segunda parte desta tese tem como objetivos: analisar a relação entre as mudanças no BSI e as respostas BOLD durante tarefas múltiplas (execução motora ou IM). Pretendeu-se ainda avaliar os mecanismos neuronais subjacentes à melhoria da função do membro superior após uma intervenção de FT e testar se a associação de um treino de IM com neurofeedback a um programa de FT pode aumentar ainda mais a eficácia deste último na neuroplasticidade e na recuperação da função do membro superior. Descobrimos que o tempo após o AVC correlaciona-se negativamente com a atividade do cerebelo contralesional e, que as mudanças nos padrões de ativação BOLD estão relacionadas com a variação do BSI, sendo diferentes do lado afetado em comparação com o movimento da mão não afetada e durante a execução em comparação com a IM. Parece que um programa de FT, durante 4 semanas, promove a recuperação da função do membro superior e neuroplasticidade, em particular nas áreas precentral e poscentral ipsilesionais, assim como no cerebelo contralesional. O treino de IM guiado através de neurofeedback real a partir de um BCI pode ajudar a melhorar a função do membro superior e simetria cerebral em comparação com um neurofeedback *sham*, em doentes com AVC crónico, contudo, as conclusões devem ser cuidadosamente tomadas. Em conclusão, a FT pode mudar a função do membro superior e a neuroplasticidade em doentes com AVC crónico; o treino de IM guiado através do neurofeedback do BCI pode ser um tratamento adjuvante uma vez que não só melhora a função do membro superior, mas também a simetria cerebral. Ensaios maiores, associando a FT ao treino de IM com um BCI, nesta população são justificados.

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Abbreviation List

9-HPT - 9-Hole Peg Test

ARAT- Arm Reach Assessment Tool

BCI- Brain-Computer Interface

BI - Barthel Index

BOLD - Blood Oxygenation Level Dependent

BSI - Brain Symmetry Index

CIMT - Constraint Induced Modified Therapy

CRBL - Cerebellum

CS - Case Series

CT - Computed Tomography

EEG – Electroencephalography

FES - Functional Electric Stimulation

FMA - Fugl-Meyer Assessment Scale

fMRI – Functional Magnetic Resonance Imaging

FR - Functional Rehabilitation

GAS - Goal Attainment Scale

m0 - Baseline Moment

m1 - Moment Before Intervention

M1 - Primary motor cortex

m2 - Moment After Intervention

MAL - Motor Activity Log

MAS - Motor Assessment Scale

MASh - Modified Ashworth Scale

MCA – Medial Cerebral Artery

MCID - Minimal Clinical Important Difference

ME - Motor Execution

MEG - Magnetoencephalography

MI – Motor Imagery

MMSE - Mini Mental State Examination

MoCA - Montreal Cognitive Assessment

MP – Mental Practice

MR - Magnetic Resonance

mRS - modified Rankin Scale

nA - Not Applicable

NIHSS - National Institute of Health Stroke Scale

OT - Occupational Therapy

P1 - Parietal Superior

PAL - Pallidum

PARC – Paracentral

PMC - Premotor cortex

PostC - Postcentral

PP - Physical Practice

PrC - Precentral

PSD - Power Spectral Density

PT - Physical therapy

PUT - Putamen

RCT - Randomized Control Trial

ROI – Region of Interest

ROM - range of motion

RR - Robotic Rehabilitation

RTP - Repetitive, Task specific, Practice

S1 - Primary Somatosensory Cortex

SIAS - Stroke Impairment Assessment Set

SIS – Stroke Impact Scale

SMA - Supplementary Motor Area

THAL - Thalamus

tDCS - Transcranial Direct Current Stimulation

TUG - Timed Up and Go

UL – Upper limb

WMFT - Wolf Motor Function Test

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Chapter 1

Introduction

Context of the work and aims

Context of the work and aims

Stroke is not only the third leading cause of death but also the most common chronic disability and Portugal is not an exception. Moreover, approximately 30% to 69% of stroke survivors have upper limb (UL) impairment. The recovery process of UL function is one major goal of neurorehabilitation (Page, Levine, & Khoury, 2009).

Although most rehabilitation programs focus on the acute phase, evidence that neuroplasticity occurs in both acute and chronic phases, supports a rationale for a continued investment in these patients (Rossini, Calautti, Pauri, & Baron, 2003). Neuroplasticity changes occur in the primary motor cortex (M1), the premotor and cingulate motor cortex (PMC) and supplementary motor area (SMA), which are related to recovery (Carey et al., 2006).

After stroke, activity-dependent plasticity can affect the nervous system both positively or negatively (Wolpaw, Birbaumer, McFarland, Pfurtscheller, & Vaughan, 2002). Since changes in cortical representation are use-dependent, neuroplasticity can be stimulated by neurorehabilitation strategies including repetition, functional goal-directed activity and attention during learning (Pomeroy & Tallis, 2002).

Motor rehabilitation, for the neurological impaired patients treatment, has traditionally focused on conventional therapy, such as physiotherapy based on the Bobath Concept (PT) (Graham, Eustace, Brock, Swain, & Irwin-Carruthers, 2009; Kollen et al., 2009; Luke, Dodd, & Brock, 2004; Tyson, Connell, Busse, & Lennon, 2009; Tyson & Selley, 2007; Vaughan-Graham, Cott, & Wright, 2014). The aim of this therapy is improving movement efficiency and promoting the generalization to daily tasks, throughout the evaluation of movement components and primary impairments (Graham et al., 2009) as well as the analysis of the problems within functional activities and the participation in daily life (Kollen, et al., 2009). Although this approach is one of the most widely used interventions in neurorehabilitation (Tyson, et al., 2009) with good results in clinical practice, there is a lack of supportive data from well controlled trials (Paci, 2003; Pomeroy & Tallis, 2002). Despite the lack of evidence concerning the effectiveness of this therapy in stroke, described in three systematic reviews (Kollen, et al., 2009; Luke, et al., 2004; Paci, 2003), there is also no evidence of its non-efficacy (Paci, 2003; Pomeroy & Tallis, 2002; Vaughan-Graham, et al., 2014). The PT focused its intervention on neuroscience, biomechanics and motor learning theories. Moreover, motor learning is related with neuroplasticity, because it leads to dendrites sprouting, new synapses formation, alteration in existing synapses and neurochemical production (Arya, Pandian, Verma, & Garg, 2011; Raine, Meadows, & Lynch-

Ellerington, 2009). Changes are expected in cortical representation and therefore neuroplasticity which is use-dependent regarding this therapy (Pomeroy & Tallis, 2002).

Newer methods, including motor imagery (MI) and brain-computer interface (BCI) are gaining popularity in neurorehabilitation in recent years. Adjunctive treatments such as MI have become part of the PT intervention (Tyson, et al., 2009). Practice of MI is defined as the internal rehearsal/simulation of an action without any evident physical movement (Sharma, et al., 2008; Page, et al., 2009). Evidence suggests that MI and movement execution activate a similar set of brain structures (Lacourse, Orr, Cramer, & Cohen, 2005; Weiss et al., 1994). MI seems to be capable of positive transfer to physical action, thus increasing motor skill learning and performance (Page, et al., 2009). After stroke, MI can temporarily improve paralyzed limb motor functions (Wang et al., 2010). Both MI and physical practice can lead to enhancing UL function in stroke patients (Prasad, Herman, Coyle, McDonough, & Crosbie, 2010). Nonetheless, there is much controversy concerning the benefits on partially recovered chronic patients of MI alone (Sharma et al., 2009), or if it is enough to induce recovery. Page and collaborators state that MI should be complemented by other evidence-based motor rehabilitation approaches, such as physical or occupational therapy (Page, et al., 2009). Nevertheless, when applying MI to motor rehabilitation, one main concern is how to ensure if mental activity is being adequately performed (Kaiser, Kreilinger, Muller-Putz, & Neuper, 2011). To address such difficulties, there have been some attempts to combine MI-based MP with BCI.

BCI are devices based on several acquisition machines that are capable of analyzing the brain activity of a specific patient and transforming it into visual, auditory and/or proprioceptive information, which is then given back to the patient, in a procedure known as neurofeedback. Notwithstanding the recently development of BCI technology, little research has been performed in stroke patients, even less so in randomized controlled trials (Prasad, et al., 2010). BCI are mostly applied to communication and control applications (Wolpaw, et al., 2002). Several authors suggest that MI EEG-based BCI training induces neuroplasticity, thus directly influencing the cortical activity and reestablishing the normal cortical activation pattern (Varkuti et al., 2013; Wang, et al., 2010).

Chapter 1.2 is a review of recent advances and proposes alternatives for future research in MI and BCI and its impact in neuroplasticity and recovery.

Recently, the measure of brain function using functional magnetic resonance imaging (fMRI) coupled with electroencephalography (EEG) is performed together with clinical outcomes

to assess recovery. However, some controversy remains regarding the correlations between these (Finnigan & van Putten, 2013; Yuan et al., 2010). In order to interpret the results obtained in terms of neuroplasticity and predict behavioral gains, we also analyzed the relationship between brain symmetry index (BSI) and blood oxygen level-dependent (BOLD) changes modulated by multiple tasks (ME and MI), for both the affected/unaffected hand in chronic stroke patients. This is different from previous studies, which use resting conditions, one task in stroke or multiple tasks in healthy subjects (see Chapter 2.1).

To understand if PT can change neuroplasticity in chronic stroke patients, we performed a pilot study where we started to compare healthy subjects with stroke patients in order to assess if our results were in line with the literature since there were few patients, by using an EEG-fMRI paradigm in a longitudinal study. Afterwards we compared the effect of 4 weeks of PT intervention in the same patients (see chapter 2.2).

It is relevant to do more research on new combined approaches, such as PT with MI EEG-based BCI in stroke rehabilitation since there are few studies, the majority of which use robotics, an expensive and not easily accessible resource (Buch et al., 2008; Prasad, et al., 2010). Consequently, the main aim was to analyze the effect of a combined intervention between PT and MI guided through neurofeedback in patient recovery and functional brain activity (see chapter 2.3).

The final part summarizes our findings and discusses not only how PT can interfere with upper limb recovery and neuroplasticity in chronic stroke patients but also how a BCI training program can increment it.

In summary, the objectives were to:

1. Analyze the relationship changes in alpha/beta brain symmetry index (BSI) and BOLD responses during motor execution or motor imagery (affected/unaffected hand) correctly for age, months post-stroke, baseline upper limb function in chronic patients.
2. Assess the neural mechanisms underlying the improvement of upper limb function after PT.
3. Assess whether the association of a MI with neurofeedback EEG-based BCI to a PT program can further enhance the efficacy of the latter in neuroplasticity and in the recovery of upper limb function in chronic stroke patients.

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The Future of Mental Practice in Stroke Recovery

The Future of Mental Practice in Stroke Recovery: A Review

Abstract

Mental practice is being increasingly used to promote recovery in stroke patients, but its benefits remain controversial. Technologies such as brain-computer interfaces are able to guide mental practice, in particular motor imagery performance. The purpose of this review is to provide a status report regarding advances in mental practice, focusing in particular in upper limb motor recovery, allied or not to a brain-computer interface. We reviewed papers on mental practice interventions in stroke patients, with or without a brain-computer interface, with upper limb assessment as primary outcome measure. This review discussed the factors that affect the ability to undergo mental practice and the changes in brain activity and function during motor imagery. From these studies, seventeen are randomized controlled trials; eight of which used a brain-computer interface. Information about study characteristics, outcomes and main motor imagery strategies and neurofeedback are described and summarized. We found that the main strategy adopted was motor imagery involving familiar tasks, which only seemed beneficial in chronic stroke patients, specially associated with other forms of intervention. Neurofeedback training with brain-computer interface systems seems to promote clinical and neurophysiologic changes in stroke patients.

Keywords: MENTAL PRACTICE, MOTOR IMAGERY, BRAIN-COMPUTER INTERFACE, BRAIN-MACHINE INTERFACE, STROKE

Introduction

Stroke is not only the third leading cause of death, but also the most common cause of chronic disability. Although approximately 80% of stroke patients survive (Page, Levine, & Leonard, 2007), most manifest some type of deficit, particularly motor. Motor rehabilitation has traditionally focused on conventional therapies (e.g. physical therapy) however newer methods, including mental practice (MP) and brain-computer interface (BCI) are gaining popularity. The aim of the present paper is to review recent advances and propose alternatives for future research in the field.

Given its success in enhancing the performance of athletes (Jeannerod, 1995; Schuster et al., 2011) and an increasing understanding of its neurobiological substrates (Sharma & Baron, 2013; Sharma, Jones, Carpenter, & Baron, 2008; Weiss et al., 1994), there has been a growing interest in applying motor imagery (MI)-based MP to motor rehabilitation (Butler & Page, 2006; Sharma, Pomeroy, & Baron, 2006). MI-based MP consists of a conscious motor representation, i.e. a structured and purposeful repetition of movements using imagination, without any motor output or evident motion (Arya, Pandian, Verma, & Garg, 2011; Jeannerod, 1995; Saimpont, Pozzo, & Papaxanthi, 2009; Sharma et al., 2008; Sharma et al., 2006). Despite this, MI shares several cognitive aspects with motion/action (Jeannerod, 1995; Page, Levine, & Khoury, 2009; Page et al., 2007; Sharma et al., 2009), and has a similar causal role in generating a specific motor activity. Importantly, this underlies its ability to contribute to motor recovery. When applying MI to motor rehabilitation, one main concern is how to ensure if mental activity is being adequately performed. Indeed, the “mental” nature of the task, makes this verification difficult both for the therapist, who has no access to the patient’s mind, and the patient him/herself, who receive no feedback regarding performance (Kaiser, Krelinger, Muller-Putz, & Neuper, 2011). To address such difficulties, there have been some attempts to combine MI-based MP with BCI. These are devices, based on functional magnetic resonance imaging (fMRI), transcranial direct current stimulation (tDCS), magnetoencephalography (MEG) or electroencephalography (EEG) capable of analysing the activity in a patient’s brain and transforming it into visual, auditory and/or proprioceptive information, which is then provided back to the patient, in a process known as neurofeedback. If MI-based MP contributes to re-establishing motor function by inducing activity-dependent brain plasticity, the use of BCI can further enhance neuroplasticity by affecting motor learning, i.e., promoting closer attention to a motor task or requiring the

activation or deactivation of a specific brain signal (Daly & Wolpaw, 2008; Dobkin, 2007). Therefore, according to a review (Wang, Collinger, et al., 2010), BCI systems have the potential to promote functional recovery after stroke given its capacity to provide real-time neurofeedback, which improves user performance in both function and BCI. However, despite this and the great development of BCI technology in recent years, little research has been carried out in stroke patients, even less so in controlled interventional studies (Prasad, Herman, Coyle, McDonough, & Crosbie, 2010).

1. What affects the ability to undergo Motor Imagery?

While aging and male gender are two risk factors for stroke, they are also key determinants of the ability to undergo MI. Undoubtedly, the ability to mentally simulate upper-limb movements has been shown to decline with aging, and this is greater for movements of the non-dominant side compared to those from the dominant one (Saimpont, et al., 2009). Contrarily, male gender seems to facilitate MI, perhaps due to gender differences in the capacity for visuospatial/visuomotor processing (Schaechter & Perdue, 2008; Schuster, et al., 2011).

MI also depends on the perspective adopted by the subject regarding the imagined movement, a matter of interpersonal variability. Indeed, effective MI requires a first-person perspective, related either to the individual's view of the imagery content or its kinaesthetic sensation (for review see (Dijkhuizen et al., 2003)), while a third-person perspective of a movement recruits mainly non-motor mechanisms (Sirigu & Duhamel, 2001) and is less likely to contribute to recovery.

In the case of stroke patients, MI also depends highly on lesion location. It is known, for example, that parietal lesions can affect either motor execution or idealization, in particular, the left parietal cortex, which is most often associated to one's attention throughout a motor action (Sirigu et al., 1996; Ward, Swayne, & Newton, 2008), similarly, dominant hemisphere lesions and neglect had less ability to produce MI (Vromen, Verbunt, Rasquin, & Wade, 2011). In addition, there are also differences in MI ability between cortical or subcortical strokes, since the latter may leave intra-cortical circuitry undamaged, hence permitting cortical reorganization to compensate functional deficits (Luft et al., 2004). Furthermore, it is known that widespread brain activity when trying to move a paretic limb occurs more commonly in subcortical strokes than in cortical ones. Given the above, in theory, a subject who suffers a subcortical stroke, in which the primary motor cortex (M1) or the parietal lobe are not involved, is likely to benefit more from early MI training than a patient with a stroke involving the cortex (Sharma, et al., 2006). Interestingly, it seems

that dysfunctions of M1 do not seriously impair the ability to perform MI, at least of the visual type (Hanakawa, Dimyan, & Hallett, 2008). Nevertheless, if the chosen outcome measure is a fMRI assessing brain plasticity, the activations will be different according to the infarct being subcortical or cortical (for review see (Calautti & Baron, 2003; Rossini, Calautti, Pauri, & Baron, 2003; Schaechter & Perdue, 2008)).

2. Brain activation during Motor Imagery

MI is thought to be a hidden stage of an executed action, occurring in cortical areas (Wang, Yu, et al., 2010). Although this interpretation is still a matter of debate (letswaart et al., 2006; Page, et al., 2009; Sharma, et al., 2006), experimental evidence, including that of a recent paper using fMRI (Sharma & Baron, 2013), suggests that MI shares the same neural substrates as movement execution. Indeed, authors of this study found numerous independent-components, i.e. cortical networks, shared between MI and motor execution in healthy subjects, especially in M1 contralateral to the movement. In line with this, data from several researchers have shown that during MI, there is a similar involvement of areas where motor planning occurs (including the supplementary motor area (SMA) and the premotor cortex (PMC)) (Butler & Page, 2006; Page, et al., 2009; Sharma, et al., 2006), however less activation of the primary motor areas occurs when compared to action (Hanakawa, et al., 2008; Jeannerod, 1995; Sharma, Simmons, et al., 2009; Weiss, et al., 1994). More importantly, similarities between both imagination and execution were also shown to extend to the balance between ipsi and contralateral regions (Sharma, et al., 2008). Interestingly, this identification between MI and motor execution might be disrupted in stroke patients. Well-recovered patients with subcortical stroke presented a disorganized activation of the ipsilesional cortical motor network during MI, but not upon executed movement (during which was similar to controls and to the non-lesioned side) (Sharma, Baron, & Rowe, 2009). This finding is in accordance with data from several researchers revealing that, when compared to the executed movement, imagined movements of the affected limb activate not only the dorsal and the medial PMC but also a wider variety of motor related regions (Butler & Page, 2006; Seitz, Matyas, & Carey, 2008). This suggests that stroke lesions, even if subcortical, alter the pattern of cortical activation induced by MI of the affected limb, although the functional significance of such alterations is still under debate (Page, et al., 2009; Sharma, et al., 2006). Several authors mentioned that an intervention targeting MI-elicited activity, i.e., controlling brain

activity, may improve motor recovery (Page, et al., 2007; Sharma, Simmons, et al., 2009), since a disorganized activity is positively correlated with residual motor impairment. Moreover, in severe patients, this alteration in activation pattern includes recruitment of additional cortical areas (Ward, 2011). If this holds true, functional recovery can be promoted rather than hampered by enhancing the MI-elicited activation pattern. This is in part, corroborated by the improvement, at least transient, in paretic limb function observed in stroke patients upon MI training (Wang, Collinger, et al., 2010). Importantly, this effect can be related to the ability of MI to induce sensorimotor cortical activity, suggesting MI to be an effective rehabilitation tool in these patients, even when volitional movements are impossible (Arya, et al., 2011; Letswaart, et al., 2006).

3. Motor Imagery in Stroke Rehabilitation

Although, there are several systematic reviews in MP associated to upper limb recovery (Barclay-Goddard, Stevenson, Poluha, & Thalman, 2011; Braun, Beurskens, Borm, Schack, & Wade, 2006; Garcia Carrasco & Aboitiz Cantalapiedra, 2013; Kho, Liu, & Chung, 2014; Nilsen, Gillen, & Gordon, 2010; Zimmermann-Schlatter, Schuster, Puhan, Siekierka, & Steurer, 2008), none have been directed to BCI or have reinforced the relation between the differences in results obtained according to the different phases (acute or chronic) or the type of MI used and its relation with a BCI system.

Several trials tried to understand the influence of MI (daily activities) (Page, 2001; Page, et al., 2009; Page, et al., 2007; Page, Levine, & Leonard, 2005; Page, Levine, Sisto, & Johnston, 2001), with greater focus on upper limb recovery in chronic patients. Generally, these studies involved small population sizes and distinct methodologies, which make comparisons and generalizations difficult. To facilitate the interpretation of results, we summarized their methodology in Table 1.

Table 1: Summary from MI studies with chronic stroke patients

Study	Study design/ Outline	Patient characteristics (age, gender and time of onset)	Functional Outcome measures	Intervention protocol and duration		MI sessions	PEDro classification
				Intervention for E/C (w/f/min)	Rehabilitation Period		
Butler & Page, 2006	CS	N=4 CIMT plus MI; n=2, 67yrs, 14mths, male; 51yrs, 16mths, female CIMT; n=1, 73yrs, 4mths, male MI; n=1, 60yrs, 3mths, male Acute and chronic phase	WMFTMAL	Combination of MI and CIMT (3h/d) CIMT (3h/d) MI alone	2wks (10 sessions)	MI not described	2/10
Page, Levine, & Leonard, 2005	RCT	N=11 MI group (n=6) Control group (n=5) 9 males, 2 females Mean age 62.3 (range, 53–71) Range, 15–48mths; average time post stroke, 23.8mths	MAL ARAT	MI group: combination of PP and MI (30min. - 5min. relaxation; 20min MI, 3–5min. refocusing), 2d/wk. Control group: PP plus sham condition (relaxation techniques - 30-min, 2d/wk.	6wks (mean 12 sessions)	Sessions emphasized daily life activities such as: i) reaching for and grasping a cup or object; ii) turning a page in a book; iii) using of a writing utensil properly; iv) using an eating utensil properly; v) using a hairbrush or comb proper.	5/10
Page, Levine, & Leonard, 2007	RCT	N=32 MI group (n=16) Control group (n=16) 18 males, 14 females Mean age 59.5 (range, 27–81) Range, 12-174mths; average time post stroke, 42.0mths	FMA ARAT				5/10

Page, Levine, & Khoury, 2009	RCT	N=10 CIMT (n=5) CIMT + MI (n =5) 7 males, 3 females Mean age 61.4 (range, 48–79) Range, 13–42mths; average time post stroke, 28.5mths	FMA ARAT	CIMT (5h/5d wk.) CIMT (5h/5d wk.) + MI (30' 3d/wk.)	10wks (30 sessions)	5/10
Page, Dunning, Hermann, Leonard, & Levine, 2011	RCT	N=29 MI20' (n=7) MI40' (n=6) MI60' (n=8) Control Group (n=8) 23 males, 6 females Mean age= 60.8 ± 12.3 (range, 21 – 76) Average time post stroke, 36.0mths	FMA ARAT	MI20' - 20min MI MI40' - 40min MI MI60' - 60min MI Control Group - RTP only 3d/wk.	10wks (30 sessions)	7/10

Abbreviations: Arm Reach Assessment Tool (ARAT); Constraint Induced Modified Therapy (CIMT);); Case Series (CS); Fugl-Meyer Scale for UE (FMA); Motor Activity Log (MAL); Motor Imagery (MI); Physical practice (PP); Randomized Control Trial (RCT); Repetitive, task specific, practice (RTP); Wolf Motor Function Test (WMFT);

Most earlier studies combined MI with other conventional therapy (Page, Levine, & Leonard, 2007; Page, Levine, & Leonard, 2005), such as constraint-induced movement or modified therapy (Butler & Page, 2006; Page, Levine, & Khoury, 2009) or involved both occupational or physical therapy (Page, 2000 cited in (Butler & Page, 2006; Page, Levine, Sisto, & Johnston, 2001)). Apart from this, there was also wide heterogeneity in reported protocols, both regarding session duration (30min average) (Page, et al., 2009; Page, et al., 2007; Page, et al., 2005), and duration of intervention (2 to 10 weeks) (Page, et al., 2007; Page, et al., 2005). Despite this, since sessions only took place 2 or 3 times/week, the mean number of sessions did not vary as much (12-30) (Page, et al., 2009). Notwithstanding these differences, groups that combined MI to other conventional therapy had significantly greater reductions in upper-limb impairment and improvement in daily activities compared to conventional therapy controls (Butler & Page, 2006; Page, et al., 2007; Page, et al., 2005). More importantly, this increase of functional recovery was accompanied by changes in cortical activation (Butler & Page, 2006; Page, et al., 2009; Page, et al., 2007; Ward, Swayne, & Newton, 2008), providing some evidence that MI can complement physical therapy to promote cortical plasticity. However, group heterogeneity regarding factors such as sample size, gender and lesion location distribution has to be taken into account when interpreting such studies.

These results encouraged authors (Page, Dunning, Hermann, Leonard, & Levine, 2011) to explore the potential of longer interventions. Remarkably, while 60min sessions were associated with greater improvement in arm function when assessed with the Fugl-Meyer Assessment Scale (FMA), but not with the Action Research Arm Test (ARAT), 20min sessions seemed to have a greater impact in the latter. Although they could be due to gender differences among groups, these results are in line with those presented by (Dickstein & Deutsch, 2007) in healthy volunteers revealing a negative correlation between the effect of MI and its duration. In light of this evidence, the same authors propose that an optimal training protocol for stroke patients should last approximately 12 to 15 minutes. In an alternative approach (Simmons, Sharma, Baron, & Pomeroy, 2008), the intervention was split in two 20min sessions, according to the daily dose of MI tolerated by patients, in order to avoid fatigue and attention deficits.

Studies in the acute or subacute phases of stroke recovery are summarized in Table 2.

Table 2: Summary from MI studies of patients in an acute or subacute phase

Study	Study design/ outline	Patient characteristics (age, gender, time of onset)	Functional Outcome measures	Intervention protocol and duration		MP Sessions	PEDro classification
				Intervention for E /C (w/f/min)	Rehabilitation Period		
Braun et al., 2010	RCT	N= 36 MI group (n= 18) Control group (n= 18) 14 male, 22 female Mean age= 77.8 Mean range: 4.8 to 6.1 wks. post stroke	BI	Both groups received multi professional rehabilitation MI Group- embedded MI in every session	6wks (at least 10 sessions)	Taught MI techniques and principles to be embedded in every session, such as walking and drinking	7/10
Bovend'Eerd, Dawes, Sackley, Izadi, & Wade, 2010	RCT	N=30 MI group - (n=15) Control group - (n=15) Several pathologies Stroke (n=28), traumatic brain injury (n=1), multiple sclerosis (n=1) 19 male, 11 female Mean age=50 Mean average range time from onset= 15.9 to 21.8wks	Motricity Index BI; Rivermead Mobility Index TUG, ARAT, Nottingham Extended ADL scale	MI group - PP or OT + MI film Control - PP or OT + PP film 3d/wk. for the first 3wks and 2d/wk. for the last 2wks	6wks (mean 6.5 hrs)	MI films - information on MI and the MI strategy. Physical practice films - general information about rehabilitation and motor learning.	8/10

letswaard et al., 2011	RCT	<p>N=102</p> <p>MI group (n=39)</p> <p>Control group_1 (n=31)</p> <p>Control group_2 (n=32)</p> <p>75 male, 51 female, mean age range: 64.4 to 69.3</p> <p>Mean range: 80.5-90.8 days post stroke</p>	ARAT Grip Strength	<p>MI group - training in MI</p> <p>Control group_1 - equally intensive training involving other forms of mental rehearsal non related to motor control</p> <p>Control group_2 - normal care with no additional training</p> <p>MI and Control group_1 received 45-min. supervised sessions 3d/wk. and 30' 2d/wk. independent sessions.</p> <p>All interventions in combination with conventional therapy</p>	4wks (12 supervised and 8 independent structural sessions)	MI of a variety of elementary movements, goal directed movements and activities of daily life	7/10
Kim & Lee, 2015	RCT	<p>N=24</p> <p>MI (n=12)</p> <p>4males, 8 females</p> <p>mean age:64.2</p> <p>mean post stroke:8.1mths</p> <p>Control (n=12)</p> <p>5males, 7 females</p>	FMA WMFT	<p>Conventional therapy 30' 5d/wk.</p> <p>+</p> <p>MI - 30' 4d/wk.</p>	4wks (12 sessions)	<p>18 tasks</p> <p>e.g. drinking from a cup, setting a seal, turning pages, brushing teeth with a toothbrush and toothpaste using both hands, making a phone call, placing a card in their wallet, changing batteries, opening and closing a zipper wallet, using scissors, spraying water, turning a faucet on and off, opening</p>	6/10

		mean age:59.4 mean post stroke:8.5mths				and closing a square airtight container, opening a bottle	
Liu, 2009	RCT	N=34 FR (n=17) MI (n =17) 21 men, 13 women, mean age: 69 Average time post stroke: 12.3 days	FMA	FR - OT and PT MI - PT + MI 1h 5d/wk.	3wks (15 sessions)	Patient self-reflection from their abilities and deficiencies: mentally imagining then performing the task.	6/10
Riccio, Iolascon, Barillari, Gimigliano, & Gimigliano, 2010	Randomized cross-over trial	N=36 Group A (n=18) Group B (n =18) 21 men, 15 women, mean age: 60.1 (range, 32–75) Average time post stroke: 7.39 wks.	Motricity Index Arm Functional Test: time Arm Functional Test: Functional Ability Scale	3wks of conventional therapy (therapeutic exercises plus OT) 3h/days 5d/wk. alone or with additionally 60min MI (twice a day) Cross-over trial: after 3 wks., groups switched	6wks from these, 3wks of MI (15 sessions)	Alone in a quiet room, performed MI by listening to an audio CD asking participants to imagine upper limb activities which were taken from the Arm Functional Test	5/10

Abbreviations: Arm Reach Assessment Tool (ARAT); Barthel Index (BI); Case Series (CS); Constraint Induced Modified Therapy (CIMT); Fugl-Meyer Scale for UE (FMA); Functional Rehabilitation (FR); Motor Activity Log (MAL); Motor Imagery (MI); Occupational Therapy (OT); Physical practice (PP); Physical therapy (PT); Randomized Control Trial (RCT); Repetitive, task specific, practice (RTP); Timed Up and Go (TUG); Wolf Motor Function Test (WMFT)

The MI programs lasted 3 (Liu, 2009) to 6 weeks (Bovend'Eerd, Dawes, Sackley, Izadi, & Wade, 2010; Braun et al., 2010; Braun, Wade, & Beurskens, 2011) and were either added (Bovend'Eerd, et al., 2010; Ietswaart et al., 2011; Ietswaart et al., 2006; Kim & Lee, 2015; Liu, 2009) or embedded in conventional therapy (Braun, et al., 2010; Braun, Wade, et al., 2011). In contrast to studies in chronic patients, MI was more often generalized (Braun, Beurskens, Kleyen, Schols, & Wade, 2011; Braun, et al., 2010), more complex (Kim & Lee, 2015; Liu, 2009) and not totally centred on upper limb. Moreover, some experimental groups received pre-training in MI performance (Bovend'Eerd, et al., 2010; Ietswaart, et al., 2011).

Results of trials in the acute or subacute phases were highly variable and sometimes contradictory. Initial studies often failed to reach meaningful conclusions due to a combination of subject heterogeneity, absence of guidance on MI performance and lack of confidence on treatment efficacy for both patient and therapist (Bovend'Eerd, et al., 2010). Despite these difficulties, a study on 34 patients (Liu, 2009) proposed that MI added to physiotherapy, enhanced a patient's ability to generalize the learned skills to other tasks while a cross-over trial with 36 subjects (Riccio, Iolascon, Barillari, Gimigliano, & Gimigliano, 2010) suggested that it also improved functional outcomes. Recently, both statistical and clinical changes in FMA in MI group compared to exclusive conventional therapy were found when using several upper limb tasks (Kim & Lee, 2015). On the contrary, a study on 36 patients with similar post-stroke time (Braun, et al., 2010; Braun, Wade, et al., 2011) failed to reveal an advantage of adding MI to conventional therapy in what regards speed and extent of recovery, when compared with conventional therapy alone. Additionally, the fact that a large study (N=102) that only compared MI to other forms of MP or normal care separately also presented negative results (Ietswaart, et al., 2011), strongly suggesting that, at least in subacute patients, MI alone is not effective and might need to be combined with other forms of rehabilitation. Some authors of studies with negative results (Braun, et al., 2010) question the amount of input given to patients to correctly perform the task, but this seems similar across studies, some of which had a positive outcome (Page, Dunning, Hermann, Leonard, & Levine, 2011), and is unlikely to be a significant factor. On the contrary, an important contributor to discrepant results is the difficulty in assessing whether the patient is actually performing MI correctly. In fact, while in most studies MI is part of the rehabilitation program, the physiotherapist has no means to independently determine patient compliance (apart from the patients' own statements). This led (Bovend'Eerd, et al., 2010) to

recognize the difficulty of integrating MI in clinical practice and highlight the need for new tools to help therapists/patients control MI execution, including BCI.

Methodological considerations notwithstanding, studies in chronic (Page, Levine, & Khoury, 2009; Page, Levine, & Leonard, 2007; Page, Levine, & Leonard, 2005) and acute/subacute (Ietswaart, et al., 2011) patients are profoundly different even in the nature of the disorder itself. Indeed, since spontaneous recovery may happen during the first few months (Rossini, Calautti, Pauri, & Baron, 2003) after stroke, the impact of interventions in acute/subacute phases may be underestimated due to spontaneous recovery. On the contrary, recovery during the acute phase can vary significantly even in patients with similar initial clinical severity, thus complicating things further (Carey & Seitz, 2007; Rossini, et al., 2003). While it has been shown that motor recovery during the first 3 months after stroke is associated with increased motor excitability of the affected cerebral hemisphere, this augmented activity seems not to be affected by any intervention (Dromerick et al., 2009). Finally, one has to bear in mind that cognitive impairment and fatigue, which are common consequences of stroke, particularly in the acute phase, have a profound impact in recovery (Kutlubaev et al., 2013; Miller et al., 2013; Prasad, Herman, Coyle, McDonough, & Crosbie, 2010). Since MI demands a great amount of attention, participants may get tired and pay less attention during the session, thus decreasing its potential benefit. Furthermore, patients are often fatigued, particularly women, which makes rehabilitation difficult and aggravates the prognosis (Kutlubaev, et al., 2013). Due to all these difficulties, it has been proposed that studies addressing brain reorganization (especially those with fMRI assessment) in response to therapeutic intervention should be, at least in the near future, mostly performed in the chronic phase of stroke recovery, to avoid the probability of spontaneous recovery (Rossini, et al., 2003). Nonetheless, this does not mean that it is not valid for acute or subacute phases.

Besides timing of lesion, there are other important differences in the major published studies of MI in chronic (Page, et al., 2009; Page, et al., 2007; Page, et al., 2005) and acute/subacute (Ietswaart, et al., 2011) stroke, which might contribute to the discrepant findings and merit further discussion. As an example, while some studies (Page, et al., 2009; Page, et al., 2007) focused on lesion in the dominant hemisphere, others (Ietswaart, et al., 2011) mainly recruited patient with non-dominant hemisphere lesions (particularly in the MI group). Functional recovery is easier in dominant compared with non-dominant limbs (Sharma & Baron, 2013), which can be related to enhanced activity-dependent brain plasticity, although this is contested by other

authors (Calautti et al., 2007). Age is another important contributor to the efficacy of an intervention, since older patients seem to have more difficulty in correctly performing MI. Unfortunately, even though studies in chronic patients (Page, et al., 2011; Page, et al., 2009; Page, et al., 2007) recruited younger subjects than those with acute/subacute stroke (Braun, et al., 2010; Ietswaart, et al., 2011) none screened patients for their ability to engage in MI (Sharma & Baron, 2013; Sharma et al., 2009). Gender might also be an issue. While male subjects are better imaginers than females, it is still not clear whether they benefit more from MI in stroke rehabilitation (Braun et al., 2013; Carey & Seitz, 2007; Ward, Swayne, & Newton, 2008) and clearly more studies are needed. It is noteworthy, however, that while studies in chronic stroke patients, that mainly recruited males, had positive results, studies in acute patients, in which recruitment was balanced regarding gender, did not (Braun, et al., 2010; Ietswaart, et al., 2011). Another difference between the most important studies mentioned above regards stroke severity. Indeed, while studies with positive outcomes (Page, et al., 2011; Page, et al., 2009; Page, et al., 2007; Page, et al., 2005) recruited patients with mild to moderate upper limb deficits, a large study with negative results (Ietswaart, et al., 2011) made no reference to the severity of their patients. Since recovery tends not to occur or be slower with greater variability (Riley et al., 2011) in patients with more severe strokes, a study recruiting such patients would have more difficulties in showing positive results, particularly in shorter interventions. In addition, outcome measures have to be appropriately chosen, since the effects of MI on velocity, precision and coordination of movement, although clinically relevant, might not be detectable with conventional assessment (Braun, et al., 2013). It has been shown that movement execution before MI interferes positively with its performance (Riley, et al., 2011; Sharma, et al., 2009) and it is conceivable that consolidating previously executed movement during MI (as opposed to exercise it after MI) might favour recovery. Finally, it also seems that when MI is directed towards a specific goal, such as upper limb rehabilitation (Page, et al., 2007), the results show more efficacy than when MI is applied to a more generalized therapy, i.e. involving all body intervention (Ietswaart, et al., 2011).

Overall there are still more doubts than certainties and many controversies remain regarding the ability of MI to promote a faster and greater improvement in motor function in stroke patients. While most authors propose this might be the case (Barclay-Goddard, Stevenson, Poluha, & Thalman, 2011; Braun, Beurskens, Borm, Schack, & Wade, 2006; Zimmermann-Schlatter, Schuster, Puhan, Siekierka, & Steurer, 2008), the poor quality and heterogeneity of published

research should make us cautious in drawing conclusions. To overcome some of the shortcomings of published studies, in particular, the lack of control over current MI practice, due to the fact that it is a mental process, as mentioned above, researchers started using BCI as a complement to interventions, and thus studies covering this will be addressed in the following section. However, the question remains, does the source of motor recovery derive from the neurofeedback from BCI or from the MI itself?

4. Brain–computer interface in neurological rehabilitation

4.1. Brain signals for Brain–computer interfaces

BCI experimental research has been primarily based on EEG and applied mostly on communication and control applications (Wolpaw, Birbaumer, McFarland, Pfurtscheller, & Vaughan, 2002). The alpha rhythm is one of the starting points in the analysis of a clinical EEG. There are different rhythms depending on the brain area and behavioural state. In particular, mu (8–12 Hz, included in alpha frequency range) and beta (12–30 Hz) rhythms, both recorded over sensorimotor cortex, decrease during not only the planning and execution of contralateral movement but also during MI (Buch et al., 2008; Neuper, Scherer, Wriessnegger, & Pfurtscheller, 2009) and have been the preferred source of information for developing assistance devices for motor disabled patients. Recently, motor related rhythms have also been applied to feedback methodologies for the enhancement of MI tasks (Buch, et al., 2008; Daly & Wolpaw, 2008; Prasad, et al., 2010).

4.2. BCI and Neurorehabilitation

Few BCI studies have been conducted in stroke patients (Ang, Chua, et al., 2015; Buch, et al., 2008; Caria et al., 2011; Prasad, et al., 2010; Ramos-Murguialday et al., 2013; Varkuti et al., 2013) and their purposes have been quite distinct. While some of them tried to select the optimal amount of EEG channels in order to decrease costs and increase specificity and accuracy of rhythm modulation by stroke patients (Tam, Tong, Meng, & Gao, 2011), others have tried to define the best way to carry out a reliable detection of motor intention (Ang et al., 2011; Niazi et al., 2011). The most popular BCI systems used in stroke rehabilitation are based on EEG, and feedback is usually visual, (either abstract (Prasad, et al., 2010) or realistic (Neuper, et al.,

2009)), or a combination of visual feedback with the control of an orthosis/robotic limb (Ang, Chua, et al., 2015; Ang et al., 2010; Buch, et al., 2008; Caria, et al., 2011; Kasashima-Shindo et al., 2015; Ramos-Murguialday, et al., 2013; Shindo et al., 2011; Varkuti, et al., 2013). In this regard, there have been multiple approaches, from an orthosis that emulates hand grasping and hand-opening (Buch, et al., 2008; Caria, et al., 2011; Kasashima-Shindo, et al., 2015; Ramos-Murguialday, et al., 2013; Shindo, et al., 2011) to a robotic arm supporting the movement of the paretic limb in a forward and backward motion (Caria, et al., 2011) or conducting it towards a goal shown on a screen (Ang, Chua, et al., 2015; Ang, et al., 2010; Ang, Guan, et al., 2015; Varkuti, et al., 2013). Importantly, studies depict that independently of the feedback given, patients (acute or chronic) (Ang, Chua, et al., 2015; Ang, et al., 2010; Buch, et al., 2008), even with mild cognitive disability (Niazi, et al., 2011), can effectively control a BCI system. More interestingly, a recent study (Bundy et al., 2012) suggested that BCI-based training of the unaffected side could help restore limb function contralaterally, providing hope to patients with severe stroke who might not control a BCI using the affected hemisphere.

Overall, studies involving a BCI-system in combination with physical therapy to promote recovery from stroke are summarized in Table 3 suggest a benefit of this approach over conventional therapy (Caria, et al., 2011; Prasad, et al., 2010) not only functionally but also in terms of normalization of brain activation patterns (Caria, et al., 2011), nevertheless some have reported negative findings. One of these recruited chronic stroke patients with hand plegia that used a MEG-based BCI system to modulate the mu rhythm, with visual feedback and the opening/closing of an orthosis attached to the impaired hand (Buch, et al., 2008), and showed no functional recovery, even in patients who became very proficient in manipulating the orthosis. Regardless of these results, this study was the first to suggest that stroke patients with complete hand paralysis can learn to control a MEG-based BCI system. Contrarily, a second study using a similar approach (Shindo, et al., 2011) observed improvement in both finger function and surface EMG activity of the affected finger extensors, even in patients with little or no motor function (Shindo, et al., 2011). In line with this, a study (Ramos-Murguialday, et al., 2013) was implemented involving severe patients and a homogeneous sample (i.e., the experimental and sham groups were matched by age, gender, paretic side, and motor impairment scores).

Table 3: Summary from BCI studies in upper limb rehabilitation in chronic stroke patients

Study	Study design/ outline	Patient characteristics (age, gender, time of onset)	Outcome measures	Intervention protocol and duration		BCI sessions and neurofeedback	PEDro classification
				Intervention for E /C (w/f/min)	Rehabilitation Period		
Ang et al., 2010	RCT	N=25 Experimental - EEG- based MI-BCI with robotic feedback neurorehabilitation (n=11) RR (n=14) 16 men, 7 women, mean age: 51.8 (range 23-65) Acute and chronic phase (average time post stroke 316 days $\pm$ 237 (range 37-831)	FMA	1-hour rehabilitation sessions 3d/wk. Experimental - 136 trials RR - 3 robot-assisted runs of 320 trials (960 trials)	4wks (12 sessions)	A visual cue on a screen and another visual cue, then instructed subject to perform MI (affected) or motor execution (unaffected). Visual and Kinaesthetic and proprioceptive feedback: the MIT-Manus robot moves the affected limb towards the goal.	6/10
Ang et al., 2014	RCT	N=21 Experimental - EEG- based MI-BCI with Haptic Knob robot (n=6) Haptic Knob robot (n=8) PP or standard arm therapy (n=7) 14 men, 7 women, mean age: 54.2 Acute and chronic phase (average time post stroke 385 days $\pm$ 131 (range 181- 651)	FMA	1-hour 4 runs (30trials) Experimental - MI or passive movement Haptic Knob robot - PP PP – repetitive task training (total 120 trials) + 30min therapist-assisted arm mobilization 3d/wk.	6wks (18 sessions)	Haptic Knob robot that assisted hand grasping (open and close hand) or knob manipulation	6/10

Ang, Chua, et al., 2015	RCT	<p>N=26</p> <p>Experimental - EEG- based MI-BCI with robotic feedback neurorehabilitation (n=11)</p> <p>RR (n=14)</p> <p>16 men, 10 women, mean age: 51.4</p> <p>Acute and chronic phase (average time post stroke 297 days $\pm$238 (range 37-831)</p>	FMA	<p>1,5-hour rehabilitation sessions 3d/wk.</p> <p>Experimental - 122 trials</p> <p>RR - 960 trials</p> <p>Without standard physical therapy</p>	4wks (12 sessions)	Identical to Ang, et al. (2010)	6/10
Ang, Guan, et al., 2015	RCT	<p>N=19</p> <p>Experimental - Transcranial Direct Current Stimulation (tDCS)- based MI-BCI with robotic feedback neurorehabilitation (n=10)</p> <p>Sham tDCS (n=9)</p> <p>14 men, 5 women, mean age: 54.1</p> <p>18 subcortical</p> <p>Chronic phase (average time post stroke 1037 days $\pm$598</p>	FMA	<p>20min tDCS or sham tDCS +</p> <p>1 hour EEG-based MI-BCI with robotic feedback</p> <p>4 runs of 40 trials (total 160 trials)</p> <p>5d/wk.</p>	2wks (10sessions)	Identical to Ang, et al. (2010)	7/10
Buch et al., 2008	Controlled study or CS	<p>N=8</p> <p>Mean age range = 41.7 to 58.2</p> <p>Chronic phase (mean range 16.7 to 25.2mths post stroke)</p>	NA	<p>1 to 2 hrs 3 to 5d/wk.</p> <p>150 to 250 trials of a goal-oriented, visual feedback task</p>	<p>3 to 8wks</p> <p>(13 to 22 training sessions)</p>	Visual and Kinaesthetic and proprioceptive feedback: a mechanical orthosis attached to the paretic hand flexed and extended the	NA

						patient's fingers in a hand-grasping or hand-opening fashion.	
Caria et al., 2011	Case Report	N= 1 Male, 67 yrs., right handed, 14 mths post stroke	FMA WMFT Functional ability, Modified Ashworth Scale, GAS	20 sessions during 4wks MEG-BCI + 20 sessions during 4wks EEG-BCI Both in combination with PT (no information)	8wks (4wks MEG-BCI; 4wks EEG-BCI – 40 sessions)	Kinaesthetic and proprioceptive feedback: MEG - a mechanical orthosis attached to the paretic hand flexed and extended the patient's fingers in a hand-grasping or hand-opening fashion. EEG control drove forward and backward movements of an arm robot.	NA
Daly et al., 2009	Case Study	N=1 Female, 43 yrs., 10 mths post stroke	NA	45 min. BCI + FES (average of 75 total attempted/imagined trials and 75 total relax trials per session). 3d/ wk. + Therapy 1d/wk. (mean time, 1.6 hrs each) + 30' FES	3wks (9 sessions total)	MI consist in index finger movement. Visual and Kinaesthetic and proprioceptive feedback: the brain signal triggered FES-assisted index finger movement practice.	NA
Kasashima-Shindo et al., 2015	Non-RCT	N=18 Experimental – tDCS + based MI-BCI with robotic feedback neurorehabilitation (n=11) BCI (n=7) 14 men, 5 women, mean age: 53.5 ±12.4/48.0±9.7	FMA MAS	tDCS prior to the BCI training + 45 min BCI + Occupational Therapy	10 days (10 sessions)	Each BCI training session consisted of 3 sessions: a voluntary contraction, calibration and visual feedback training. Participants had to imagine the affected hand opening easily	5/10

		Subcortical Chronic phase (average time post stroke 1037 days $\pm$ 598)		5d/wk.			
Li et al., 2014	RCT	N=15 Experimental- BCI + FES (n=8) Control - FES (n=7) 11 men, 4 women, Age (range 60-76) Acute phase (range 1-6mths)	FMA ARAT	Experimental - 1-1.5h BCI-FES Control - 20min FES 3d/wk. + Conventional therapies 5d/wk.	8wks (24sessions)	Imagined affected versus unaffected hand movement according to a virtual game, feedback was stimulation of the affected upper extremity's extensor carpus radialis muscles	6/10
Ono et al., 2014	Non-RCT	N=12 BCI training with visual feedback (n=6) BCI training with proprioceptive feedback (n=6) 16 men, 10 women, Subcortical Age (range 41-84) Acute and chronic phase (range 4-155)	SIAS	1h 60 trials with visual feedback 5d/wk. 100 trial with proprioceptive feedback 1-2d/wk.	Visual feedback 4wks (20 sessions total) Proprioceptive feedback 4-7mths	Visual or Kinaesthetic and proprioceptive feedback	4/10
Prasad, Herman, Coyle, McDonough, & Crosbie, 2010	CS	N=5 4 males, 1female, mean age: 58.6 (8.98), (range 47-71)	Motricity Index ARAT, Nine Hole Peg Test	30' 2d/wk. MI of the movement with undamaged arm (10 times, ca	6wks (12 sessions)	MI consisted of imagining the performance of motor sequences and kinaesthetic sensations associated with it. Visual Feedback: A ball appeared on the	2/10

		Chronic stroke: mean 28 (15.4) mths post stroke (range 15-48mths)	Grip Strength	1min) + MI with damage arm (10 times, ca 1min)		top of the user window and a beep sound informed the user to attempt to place the ball in the target basket (by using his/her hand imagination).	
Ramos-Murguialday et al., 2013	RCT	N=32 Experimental - EEG- based MI-BCI with robotic feedback (n=16) Control- robotic sham movement (n=16) 18 men, 12 women, mean age: (49.3 and 50.3, experimental and control group respectively) Chronic phase (average time post stroke 66 and 71 mths, respectively)	modified FMA MAL GAS	Experimental – BCI plus PT- 275 ± 25 (runs; 1run=11trials x 5s) Control - sham-BCI plus PT - 291 ± 17 (runs) 1h of behavioural PT	4wks (20 sessions)	Kinaesthetic and proprioceptive feedback: a mechanical hand orthosis opening and closing of the hand	8/10
Shindo et al., 2011	CS	N=8 All men, mean 59 yrs. (range age: 46-68) Chronic phase (range 15 to 144 mths)	Stroke Impairment Assessment Set MAL MAS	1 hr session, 1 or 2d/wk.	4 to 7mths (12–20 sessions)	Similar to Kasashima-Shindo, et al. (2015)	6/10

Song et al., 2015	CS	<p>N=13</p> <p>8 men, 5 women, mean age: (61.9±11.41)</p> <p>Acute and Chronic phase (average time post stroke 23.4 ± 24.33 mths, range 2 to 99mths)</p>	<p>ARAT</p> <p>NIHSS</p> <p>SIS – hand function</p>	<p>2-hour BCI training</p> <p>10 runs (8-12 trials)</p> <p>2-3d/wk.</p>	6wks (15 sessions)	<p>A visual cue on a screen instructed patients to move (and not motor imagery)</p> <p>Visual feedback alone (during 10 trials) followed by FES and tongue stimulation feedback</p>	2/10
Varkuti et al., 2013	RCT	<p>N=9</p> <p>Experimental - EEG- based MI-BCI with robotic feedback neurorehabilitation (n=6)</p> <p>RR (n=3)</p> <p>7 males, 2 female, Age range (21-65yrs)</p> <p>Acute and Chronic phase (range 3,9 to 35,1mths)</p>	FMA	<p>1-hour rehabilitation sessions</p> <p>3d/wk.</p> <p>Experimental – variable trials</p> <p>RR - 960 trials (fixed)</p>	4wks (12 sessions)	<p>A visual cue on a screen, then instructed subject to perform MI (affected)</p> <p>Visual and Kinaesthetic and proprioceptive feedback: the MIT-Manus robot moves the affected limb towards the goal.</p>	6/10
Young, Nigogosyan, Remsik, et al., 2014	Non-RCT	<p>N=9</p> <p>6 males, 3 female, mean age: (62±9.2)</p> <p>Acute and Chronic phase (average time post stroke 12.9 ± 7.9 mths)</p>	<p>ARAT</p> <p>9-HPT</p> <p>SIS</p>	<p>2-hour BCI training</p> <p>10 runs (8-12 trials)</p> <p>2-3d/wk.</p>	6wks (15 sessions)	Similar Song, et al. (2015)	2/10

Young, Nigogosyan, Walton, et al., 2014	RCT	<p>N=11</p> <p>Exp - BCI therapy group (n=5+3 from crossover control)</p> <p>Control - crossover control (n=6)</p> <p>average age = 63±9.5years Exp and 56.5±10.34 Control (range 48-75)</p> <p>Acute and Chronic phase - average time post stroke= 13.13 ±8.44 mths Exp and 13±6.96mths Control (range 2-23 mths)</p>	<p>ARAT</p> <p>9-HPT</p> <p>SIS</p>	<p>2-hour BCI training</p> <p>2-3d/wk.</p>	6wks (9-15sessions)	Similar Song, et al. (2015)	5/10
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Abbreviations: 9-Hole Peg Test (9-HPT); Arm Reach Assessment Tool (ARAT); Barthel Index (BI); Brain-Computer interface (BCI); Case Series (CS); Constraint Induced Modified Therapy (CIMT); Fugl-Meyer Scale for UE (FMA); Functional Electric Stimulation (FES); Goal Attainment Scale (GAS); Modified Ashworth Scale (MAS); Motor Activity Log (MAL); Motor Imagery (MI); National Institute of Health Stroke Scale (NIHSS); Physical Practice (PP); Physical therapy (PT); Randomized Control Trial (RCT); Repetitive, task specific, practice (RTP); Robotic rehabilitation (RR); Stroke Impairment Assessment Set (SIAS); Stroke Impact Scale (SIS); Transcranial Direct Current Stimulation (tDCS); Timed Up and Go (TUG); Wolf Motor Function Test (WMFT); Not Applicable (nA)

Both these groups had a similar amount of BCI training and showed a significant improvement in hand function, but the intervention group had higher muscle activity. Of note, the authors (Ramos-Murguialday et al., 2013) considered the average gain of 3.4 points on the modified FMA in the experimental group as clinically significant, in light with a significant change in the same limb from none to some muscle activity. However, if one considers 5.2 points as the minimal clinically meaningful change in the FMA (Wagner, Rhodes, & Patten, 2008), as previously determined in chronic stroke patients, this outcome must be considered with caution. The same authors who also explored cortical activity with fMRI/EEG found an increased activity in ipsilesional cortical areas during the motor execution task in the experimental group, therefore this might be due to the different proportion of subcortical strokes (14/16 vs 7/16, experimental vs sham respectively). Moreover, there are differences in MI ability between cortical and subcortical strokes (Luft et al., 2004) that can also interfere with the ability to control a BCI system.

A clearer effect of EEG-based BCI system combined with physical practice came from a study (Prasad, Herman, Coyle, McDonough, & Crosbie, 2010) in which visual neurofeedback was provided as part of a computer game. Not only the patients improved in at least one functional outcome measure, but also the authors found a correlation between functional improvement (assessed by the ARAT) and the individual ability to control brain activity, although lack of a control group limited the relevance of these findings. Interestingly, when comparing robotic rehabilitation alone with EEG-based BCI system with robotic feedback (Ang et al., 2010), the average motor improvement found in the experimental group was slightly less than in controls. While the authors suggested that this could be due to the limited number of intervention trials, the heterogeneity of lesion sites, age and timing of stroke are also likely contributors. Recently (Varkuti et al., 2013), an improvement was described in neuroplasticity and function in both the BCI and control groups, though higher (and more variable) in the former. The authors interpreted these findings thus suggesting that BCI training strengthens neuroplasticity, which leads to better recovery. However, care must be considered because of the small sample size. Nevertheless, there were no differences in functional gains, after intervention, when comparing the exclusive use of Haptic Knob robot or if it was allied to EEG- based MI-BCI (Ang et al., 2014), but longer proprioceptive feedback intervention seems to benefit patients more compared to intensive training with visual feedback (Ono et al., 2014). Additionally and more current literature state that when comparing the combination of real tDCS (Ang et al., 2015; Kasashima-Shindo et al., 2015)

or sham (Ang, et al., 2015) with 1 hour EEG-based MI-BCI to a robotic feedback, both groups improved functionality near the MCID of FMA yet, the accuracy in controlling the BCI was higher in the former (Ang, et al., 2015; Kasashima-Shindo, et al., 2015), probably due to changes in brain activity (Kasashima-Shindo, et al., 2015). The majority (Ang, et al., 2015; Ang, et al., 2014; Kasashima-Shindo, et al., 2015) had subcortical stroke thus, one question remains: do patients still have the same results in cortical stroke? The recovery observed could either be the result of a more “normal” brain activation, in terms of lateralization, induced by the central nerve system guided through BCI or the contingent sensory input given by feedback, which increases the synaptic strengthening of reduced or previously inhibited motor networks (Ono, et al., 2014; Soekadar, Birbaumer, & Cohen, 2011).

Even though not a clinical trial, a case report (Caria et al., 2011) raised an interesting question on the comparative efficacy of EEG and MEG based systems. The authors describe a chronic stroke male patient who underwent 4-weeks of MEG-based BCI system followed by 4-weeks of EEG-based BCI system (20 sessions each) combined with physical therapy (1h/day). The neurofeedback was provided visually in combination with opening/closing of an orthosis in the case of MEG and a forward and backward movement of an arm robot in EEG. Following intervention, the patient improved upper limb function and the fMRI data showed an increased lateralization toward the ipsilesional sensorimotor regions; however, there was greater BCI performance after MEG compared to EEG training, as assessed by the success in producing the requested mu rhythm amplitude modulation. These results can be related to motivation in the initial sessions compared to the final ones or to the kinaesthetic and proprioceptive feedback given (hand opening/closing or reaching movement). Nevertheless, functional recovery only demonstrated superior to MCID after the 8-weeks therefore, the product of this single case can raise issues for further study.

In a novel approach (Daly et al., 2009), BCI was combined with functional electrical stimulation (FES) to improve hand function. Despite patients showing functional gains, it is unclear if the gains were from BCI, FES or combination of both or simply from whole arm or hand motor task practice (Daly, et al., 2009). Nonetheless, when comparing FES with or without BCI, the former increased in both hand function (in one of two outcome measures) and MI performance in the acute phase. However, no differences were found in brain symmetry between groups (Ono, et al., 2014). Contrarily, changes in functional connectivity occurred when feedback through FES was

combined with an attempted movement and which can be related with the thalamocortical circuits and/or the appropriate cortical activity encouraged by the BCI (see (Young, Nigogosyan, Remsik, et al., 2014; Young, Nigogosyan, Walton, et al., 2014)).

In summary, the studies with BCI suggest that patients with chronic or acute stroke had the accuracy to perform MI with feedback (visual, kinaesthetic and/or proprioceptive) even though volitional isolated finger movement was not possible. Nonetheless, there is no clear evidence that a BCI system does in fact improve the motor function of severe stroke patients (Buch et al., 2008). On the other hand, training with an EEG or MEG BCI system may cause neuroplasticity. However, conclusions regarding functional recovery must be carefully taken into consideration, given the extremely limited number of patients and the non-controlled nature of some studies (consisting of single case reports and case series) (Buch, et al., 2008; Caria, et al., 2011; Prasad, et al., 2010).

Conclusion

In conclusion, the main strategy of the reviewed studies was to add MI to conventional therapy where familiar tasks were carried out, predominantly from daily life. Most studies added MI to other types of therapy, while others embedded it in conventional therapy. Overall, MI training appears to have better functional results in chronic than in acute or subacute stroke (Bovend'Eerd, Dawes, Sackley, Izadi, & Wade, 2010; Ietswaart et al., 2011). Moreover, MI skill learning seems to be transferable to physical performance. This happens even if the patient cannot explicitly produce movement (Butler & Page, 2006; Page, Levine, & Khoury, 2009; Page, Levine, & Leonard, 2007; Seitz, Matyas, & Carey, 2008) and is independent of dosage times (Page, Dunning, Hermann, Leonard, & Levine, 2011). Additionally, it seems that repetitive physical practice coupled with MI can induce larger cortical changes, thus leading to cortical reorganization and functional outcome improvement (Butler & Page, 2006), at least with short-term effects. However, MI alone may not be enough to induce recovery or reinforce progress unless it is complemented with other evidence-based motor rehabilitation approaches (Arya, Pandian, Verma, & Garg, 2011; Page, et al., 2009).

Although there is evidence showing that BCI-based neurofeedback together with physical practice (conventional therapy or robots) can enhance upper limb function recovery, it is still unclear how it promotes clinical and neurophysiological changes in stroke patients (Ang, et al., 2014; Shindo et al., 2011). Therefore, more and larger studies must be carried out in order to understand if

the source of motor recovery derives from conventional therapy, MI, neurofeedback from BCI or the combination of these.

Brain-computer interface: hints for the future

As BCI and neurofeedback show promise in the rehabilitation of stroke subjects, more and higher quality research is needed in order to elucidate its effects and start to discriminate which protocols lead to the best results. In order to achieve this goal, studies should be standardized and methodologies clearly described. Hereafter, we provide some suggestions on the design of future studies regarding this topic.

Starting with inclusion criteria, several aspects need to be taken into account. As mentioned before, the characteristics of each patient (Dickstein & Deutsch, 2007) can interfere with the ability to perform a correct MI and to control a BCI system. Studies should begin with the assessment of MI ability (Sharma & Baron, 2013) in patients but also in controls. A similar proportion of males/females' participants in each group (Schaechter & Perdue, 2008; Schuster et al., 2011) and a good stratification regarding age is also critical (Saimpont, Pozzo, & Papaxanthis, 2009). The same care should be taken regarding lesion location and handedness (Carey & Seitz, 2007; Ward, Swayne, & Newton, 2008).

The time post stroke also should be considered when testing the impact of a new intervention. In our opinion, to avoid any probability of spontaneous recovery, which occurs in an acute phase, minimizing variability, chronic stroke patients should, whenever possible, be preferred (Calautti & Baron, 2003; Rossini, Calautti, Pauri, & Baron, 2003; Wang et al., 2010). Importantly, timing post-stroke has a strong influence not only on functional assessments but also on fMRI and EEG. Additionally, fatigue (Kutlubaev et al., 2013; Miller et al., 2013; Prasad, et al., 2010) is less of a problem in chronic phases, therefore reducing the interference with the ability to perform MI.

Another important focus of attention in the design of future studies of BCI on stroke rehabilitation concerns the nature of the (neuro) feedback provided to the patient. Realistic feedback, such as a virtual hand movement, might be preferable to more abstract feedback, given the possibility that observation of the virtual hand movement may itself lead to an activation of mirror neuron in the sensorimotor areas (Lucca, 2009; Pfurtscheller, Muller-Putz, Scherer, & Neuper, 2008). Indeed, Arya and collaborators (Arya, et al., 2011) show that an enriched training environment, including use of realistic feedback, helps to stimulate cortical reorganization and motor/functional

recovery. However, according to Neuper, et al. (Neuper, Scherer, Wriessnegger, & Pfurtscheller, 2009), feedback type per se (whether realistic or more abstract) does not influence the performance in BCI applications, at least in healthy subjects. While future studies should try to address which feedback modalities might produce better results, patient preferences for different feedback strategies should also be taken into account. Ideally, feedback should be tailored to the individual, considering personal preferences, but also daily needs and difficulties. By addressing each patient's problems, this strategy will greatly contribute to patient motivation leading to enhanced results.

Regarding feedback, one should also bear in mind that the correctness of the classification algorithms has a strong impact in BCI performance. Of note, this impact seems to be non-trivial, thus inaccurate feedback might result in weaker performance in healthy subjects who previously had good accuracy, but feedback distortion improves the accuracy of those who performed around chance-level (Barbero & Grosse-Wentrup, 2010).

The body of knowledge reviewed above seems to suggest that MI (with or without BCI) provides better results if used in conjunction with physical performance. In this case, the temporal relationship between MI/BCI feedback and physical performance should be precisely defined. Indeed, while MI after physical performance might reactivate recently used motor representations and thus contribute to its consolidation, it may also be hampered by patient's fatigue, an issue that must be taken into consideration.

In order to understand the effect of MI, we suggest a study with randomization into four groups, i) control (no intervention, to serve as reference to longitudinal fMRI changes due to learning), ii) only conventional therapy (to analyse therapy influence) iii) conventional therapy with simultaneous real neurofeedback and, iv) conventional therapy with sham neurofeedback. This way, researchers can conclude if the improvement derives from conventional therapy, real neurofeedback or MI itself.

In conclusion, MI seems to be a valuable intervention in stroke rehabilitation, particularly when combined with conventional therapies. More importantly, its results seem to be enhanced when it is driven by a BCI-based neurofeedback system, by which patients are encouraged and therapists informed about patient performance. Future studies will help to elucidate which MI-BCI modalities work best and allow the design of more tailored interventions.

A specific and more updated systematic review about BCI in upper limb recovery in stroke patients was performed (Annex I).

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Correlation between task-related changes in alpha/beta brain symmetry index with resting state or with BOLD responses during motor execution or motor imagery in chronic stroke patients

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Correlation between task-related changes in alpha/beta brain symmetry index with blood oxygen level-dependent responses during motor execution or motor imagery in chronic stroke patients

Abstract

There is some debate regarding electrical and hemodynamic measurements of brain activity correlations. Moreover, several other aspects must be considered seeing that they can interfere with neuroplasticity and motor recovery in stroke patients.

The relationship between task-related changes in alpha/beta brain symmetry index (BSI) with blood oxygen level-dependent (BOLD) responses was analyzed throughout motor execution and motor imagery (affected/unaffected hand) in chronic patients. Multiple regression analysis examined the correlation between BOLD signal alterations with BSI (according to task, execution or imagination of the affected/unaffected hand) correcting to age, time post-stroke and function at baseline. Time since stroke was negatively correlated with cerebellum activity. Moreover, asymmetry through left was both positively correlated with contralesional precentral, bilateral postcentral and SMA activity during task execution/imagination of the affected hand at beta frequency, and with ipsilesional precentral in imagination. However, it only occurred during imagination (contralesional precentral) at mu frequency. Throughout the execution of the unaffected hand, negative (mu frequency) or no correlation (beta frequency) occurred between contralateral precentral and postcentral areas and brain asymmetry, while negative (beta frequency) or no correlation (mu frequency) was observed in contralateral parietal and ipsilateral SMA, during imagination. BSI alterations were related to changes in BOLD activation patterns and different from the affected compared to unaffected hand movement however; they are quite similar during execution compared with the imagination of the affected hand.

Highlights

- Months post stroke interfere with contralateral cerebellum activity
- BSI correlates to BOLD changes though the affected differs from the unaffected hand
- BOLD positively correlates with EEG through the contralateral side in the affected hand
- Bilateral correlations occur in affected hand in movement/imagination at beta frequency
- Rehabilitation may be somatosensory-guided learning based on target cerebellum

Keywords: EEG-fMRI, Stroke, Correlation, Motor execution, Motor imagination

1. Introduction

Neuroplasticity is responsible for stroke rehabilitation and recovery (Cameirao, Badia, Oller, & Verschure, 2010). Though it is quicker in the first months (Taupin, 2006), it also occurs in the chronic period after stroke (Cauraugh, 2004; Fischer et al., 2007; Hara, 2015; Hodics, Cohen, & Cramer, 2006; Luft et al., 2004; Nelles, 2004; Nudo, 2003; Rossini, Calautti, Pauri, & Baron, 2003). Several factors such as stage dependency (acute or chronic), age, lesion location (cortical/subcortical or dominant/non dominant hemisphere), handedness (Carey & Seitz, 2007; Sirigu et al., 1996; Ward, Swayne, & Newton, 2008; Zemke, Heagerty, Lee, & Cramer, 2003) and severity (Serrien, Strens, Cassidy, Thompson, & Brown, 2004) interfere with the cortical reorganization. There is a lack of functional integration studies in chronic stroke (Mintzopoulos et al., 2009).

Besides clinical assessment, the measure of brain function using functional magnetic resonance imaging (fMRI) (Hodics, et al., 2006) coupled with electroencephalography (EEG) (Sheorajpanday, Nagels, Weeren, van Putten, & De Deyn, 2011; Weiss et al., 1994), is useful to predict behavioral gains from restorative therapies, since both are non-invasive and together, they complement each other in terms of spatial and temporal resolution, respectively (Carey & Seitz, 2007; Murta, Leite, Carmichael, Figueiredo, & Lemieux, 2015; Wolpaw, Birbaumer, McFarland, Pfurtscheller, & Vaughan, 2002).

Numerous motor paradigms for fMRI were described (Carey & Seitz, 2007) mentioning that activation can be detected during higher order cognitive processes, such as motor imagination (Le Bihan, 1996). Hence, a combined paradigm, i.e. not only involving a motor task but also imagination, is crucial, since the participation of the same cortical areas occurs in both imagined or executed movements (Butler & Page, 2006; Page, Levine, & Leonard, 2007; Seitz, Matyas, & Carey, 2008; Weiss, et al., 1994). Nonetheless, there are also several methods to quantify EEG, in particular frequency-specific power measures or brain symmetry index (BSI) (Finnigan & van Putten, 2013), and usually at alpha and/or beta frequency bands which have distinct roles (Brinkman, Stolk, Dijkerman, de Lange, & Toni, 2014). Alpha involves inhibition of cortical areas which are not relevant for movement to occur while beta is responsible for the disinhibition of the contralateral sensorimotor cortex. EEG background activity is a useful tool to show activation processes during not only execution but also imagination. Moreover, there are also clear changes in EEG activity during mental practice compared with EEG during a baseline period in stroke patients (Weiss, et al., 1994). Furthermore, similarly to healthy subjects, stroke patients with

good recovery had more brain symmetry (van Putten & Tavy, 2004). nonetheless asymmetry occurs due to some aspects, such as ischemia (Finnigan & van Putten, 2013). Even though few studies combine these two techniques, some controversy remains regarding the correlations between changes in pattern and degree of activation in blood oxygen level-dependent (BOLD) signal and EEG. A negative correlation between BOLD signal and alpha rhythm was mentioned, suggesting that they are a pair of antagonistic indicators for the neural activation in healthy subjects (Yuan et al., 2010). Contrarily, in a systematic review, a relatively strong positive correlation between alpha power and BOLD was cited (Finnigan & van Putten, 2013). This is why we are interested in BSI and BOLD changes modulated by multiple tasks (ME and MI), for both the affected/unaffected hand in chronic stroke patients, different from previous studies which use resting conditions, one task in stroke or multiple tasks in healthy subjects.

Therefore, we aimed to determine the relationship between task-related changes in alpha/beta BSI and BOLD responses during motor execution or motor imagery (affected/unaffected hand) controlling factors that can interfere with motor recovery (age, months post-stroke, baseline upper limb function) in chronic patients.

2. Material and Methods

2.1 Sample

Patients were recruited from the outpatient service at a Regional General Hospital after the protocol was approved by the hospital Ethics Committee. The patients with a first-ever episode of left middle cerebral artery (MCA) cortical infarct ≥ 12 months ago (and no other documented stroke), were prospectively selected. Infarct site was identified using structural MR or CT scans and classified using clinical and radiological criteria. Exclusion criteria were: persistent language and cognitive deficits (assessed by Montreal Cognitive Assessment (MoCA) and Mini Mental State Examination (MMSE)), inattention, visual impairment, depression, inability to toilet themselves independently prior to their stroke, left-handedness, inability to perform accurate motor imagery, i.e. score less than 75% in hand rotation component (see (Sharma & Baron, 2013)), and contraindications to MRI (e.g. claustrophobia or pacemaker).

All subjects were right-handed (assessed by Edinburgh Handedness Inventory) and gave written consent in accordance with the Declaration of Helsinki.

2.2 Procedures

2.2.1 Primary outcome measures

2.2.1.1 Motor and Imagery Paradigm to EEG-fMRI

The EEG-fMRI paradigm was a block design finger–thumb opposition sequence alternating either motor imagination (MI) or motor execution (ME) with rest for each hand and this was repeated five times. The initiating hand was random. ME was performed after MI, since activation patterns during MI could be influenced if preceded immediately by ME (Sharma, Baron, & Rowe, 2009). Finger movements during scanning were monitored by using individual cameras and registered based on the EMG.

2.2.1.2 EEG and fMRI data acquisition and processing

Setting: Siemens 3.0T (Siemens, Magnetom Vision, Erlangen, Germany), FoV: 245mm², spatial resolution: 3x3x3mm³, TR 3s, TE 30ms, Flip Angle: 90°, 46 slices. FMRI analysis was processed in Statistical Parametric Mapping software (SPM8 -<http://www.fil.ion.ucl.ac.uk/spm/>) using a standard pre-processing pipeline (slice timing correction, realignment, coregistration of structural and functional images, normalization and smoothing). Excessive head movement did not occur. In addition, T1-weighted anatomical images of the entire brain were obtained with the following pulse sequence parameters: FoV 256 mm²; spatial resolution: 1x1x1.2mm³; TR = 2300ms; TE = 2.98 ms; flip angle 9°; 160 slices. The first four volumes (12 s) of each fMRI session were discarded because of unstable magnetization.

We limited our analysis to a mask comprising 18 regions of interest (ROI), involved in motor execution. As we were interested in studying both lesioned and non-lesioned sides, all our regions are bilateral (i.e. right and left). Regions selected are: precentral (PrC) and postcentral (PostC) cortices, supplementary motor area (SMA), parietal superior (P1) and paracentral (PARC) cortices, thalamus (THAL), putamen (PUT), pallidum (PAL) and cerebellum (CRBL).

The EEG was acquired simultaneously with fMRI using a synchronized imaging protocol, data was continuously collected at 10kHz using a 64-channel MRI-compatible system (MagLink by Neuroscan, Division of Compumedics Ltd., El Paso, TX) with two electro-oculogram and two electrocardiogram electrodes. Electrode impedances were all kept at less than 5 kOhms. Gradient artifact and cardiac ballistic artifact were removed from the raw EEG data by means of template subtraction (Allen, Josephs, & Turner, 2000) (Vision Analyzer, Brain Products,

Germany). The EEG data was down-sampled to 250Hz, a 50Hz notch was used and then a low-pass filter of 30Hz and visual artifact rejection was also carried out.

The power spectral densities (PSD) of EEG were estimated using Welch's method. Power spectrum density was grouped into bands: mu (8–13Hz) (Finnigan & van Putten, 2013; Sheorajpanday, et al., 2011; Weiss, et al., 1994; Yuan, et al., 2010) and beta (14–30Hz) (Graziadio, Tomasevic, Assenza, Tecchio, & Eyre, 2012; Morash, Bai, Furlani, Lin, & Hallett, 2008; Pfurtscheller, Brunner, Schlogl, & Lopes da Silva, 2006) and to specify the area analysis, several pools were created (e.g. Central_left/lesioned= pool C1,C3,FC1,FC3; Central_right/non-lesioned= pool C2,C4,FC2,FC4), based on (Vecchio, Babiloni, Buffo, Rossini, & Bertini, 2013) study.

We quantified the degree of symmetry in oscillatory activity during, MI and ME (van Putten & Tavy, 2004), the differences of the PSD between the lesioned and non-lesioned corticospinal system at cortical level are divided by their sum and was expressed as the real value, which defined the brain symmetry index (BSI). (e.g. BSI during MER (BSI_MER)= $(C_left(MER) - C_right(MER)) / (C_left(MER) + C_right(MER))$). A value of +0.0 would indicate absolute symmetric activity; a value of 1 or -1 indicates unilateral activity/asymmetry, i.e. in which direction, more activity in the contralateral or in the ipsilateral hemisphere, respectively. A signal analysis was performed in several blocks, however we considered the first 10seconds of BSI changes to be the most representative.

2.2.1.3 EMG acquisition and processing

In order to control mirror movements, an EMG measurement of muscle activity from the *flexor digitorum*, of both hands, was also carried out during the fMRI paradigm. The data was collected using Acknowledge 3.9 (BIOPAC System Inc., Goleta, CA, USA) software and MP150 was used to record and process EMG measurements.

2.2.2 Behavioral assessment

Upper limb function was assessed by Action research arm test (ARAT), Fugl-Meyer assessment scale – arm section (FMA) and Motor assessment scale (MAS) (Carr, Shepherd, Nordholm, & Lynne, 1985; Croarkin, Danoff, & Barnes, 2004; van der Lee et al., 1999; Yozbatiran, Der-Yeghiaian, & Cramer, 2008) as well as handgrip strength. The grip force was measured with Baseline® Hydraulic Hand Dynamometer, with the average of three consecutive values scaled in kilogram and used for the analysis. The patient was seated with the elbow flexed 90 degrees and was not allowed to bring the instrument or arm into contact with the body, therefore having to

exert the strongest grip possible. The modified Rankin Scale (mRS) was used for measuring the degree of disability. All functional assessments were video recorded and independently scored offline by two blind assessors, with the average score between both being used for analyses.

2.2.3 Statistical Analysis

The contrast images from the first level analysis (ME and MI for right and left hand, i.e. MER, MIR, MEL and MIL, respectively) were performed in SPM8 and were used for the second level analysis, using the above-mentioned mask.

Bivariate analysis was performed to evaluate the linear relationship between every possible pair of the following measurements: functional scores, age, months post-stroke and the BSI at mu and beta frequency bands for each task (MER, MIR, MEL, MIL). We used Pearson correlation for normally distributed measurements and Spearman rank ordered correlation when normality assumptions were violated. All comparisons were considered statistically significant when $p < 0.05$.

Statistical images analysis was performed using multiple regressions to examine the correlation between BOLD signal changes during each of the 4 tasks (MER, MIR, MEL or MIL) and BSI during each of the 4 tasks, correcting for age, time post-stroke and function at baseline as nuisance variables. To separate the possible confounding effects of the time after stroke from any independent relationship of laterality index and neurologic status, we used multiple linear and ordinal logistic modeling. p values of < 0.01 combined with a minimum/critical cluster size of 117 voxels were considered significant.

3. Results

From an initial list of 102 individuals, 92 patients were ineligible: more than one event ($n=6$), other associated neurological/muscles disorders ($n=9$); visual impairment ($n=4$); complete paralysis ($n=7$); severe cognitive deficits, depression and/or CMIA $< 75\%$ ($n=9$), comprehensive aphasia ($n=11$), no functional deficits (ARAT > 51) ($n=26$), allocated to other study ($n=7$); epilepsy ($n=5$), left hand dominance ($n=1$) and finally contraindications to MRI ($n=7$). Thus, only 10 subjects were recruited due to the difficulty in finding eligible participants (Table 1).

Table 1: Patient characteristics according to age, gender, lesion location, time post stroke, upper limb function baseline (ARAT, MAS, FMA) and cognitive assessment (MMSE/MoCA)

Case	Age (years)	Gender (M/F)	Lesion Site	Time post stroke (months)	ARAT Baseline (/57)	MAS Baseline (/18)	FMA Baseline (/66)	MMSE/MoCA (/30)	mRS x/6
P1	72	M	L MCA	14	29	6	18	27/19	3
P2	61	F	L MCA	37	4	2	14	29/23	4
P3	43	F	L MCA	18	48	12	43	28/30	2
P4	66	M	L MCA	70	39	16	30	29/23	3
P5	36	F	L MCA	78	38	14	44	30/27	2
P6	61	F	L MCA	40	36	14	52	29/23	1
P7	61	M	L MCA	66	49	18	57	28/20	1
P8	63	M	L MCA	13	37	12	31	28/24	3
P9	74	F	L MCA	40	16	6	22	27/25	4
P10	52	F	L MCA	14	41	17	46	28/25	2
Mean ± sd	59±12.0	—	—	39±24.6	34±14.0	12±5.3	36±14.8	—	

Abbreviations: ARAT - Action research arm test; F-Female; FMA - Fugl-Meyer assessment scale – arm section; L-Left; M-Male; MAS - Motor assessment scale; MCA – Medial cerebral artery; MMSE - Mini Mental State Examination; MoCA - Montreal Cognitive Assessment; mRS - modified Rankin Scale

Average age at stroke was 59 years (SD = 12.0years), the average time from stroke onset was 39 months (SD = 24.6 months), ranging from middle to severe patients. All enrolled subjects completed the study assessments.

The median values of real BSI during each task are described in table 2 and 3, demonstrating that the activity was predominantly on the right hemisphere independently of being performed by affected or unaffected hand. Tables of all activated regions identified from EEG and fMRI maps are listed in the supplemental materials, including the subcortical areas (Annex II).

3.1 Correlations of age, time post-stroke and functional assessment scores with EEG-fMRI

Age and EEG / fMRI

No correlation was found between age and BOLD or BSI.

Time post stroke and EEG / fMRI

There was a negative correlation between time post-stroke and activity in cerebellum_6 right during MER, MIR and MIL ($\rho=-0.91$) independently of age and arm function (Figure 1). No other significant correlations were found between time post stroke and any fMRI or EEG parameters.

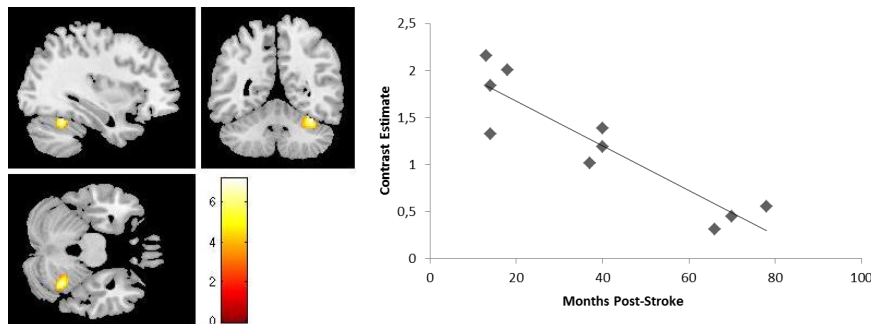


Figure 1: Cerebellum_6_R activation area correlated with time post-stroke (here shown during MER, but also during MIR and MIL)

Functional assessment scores and EEG / fMRI

As expected, the results of the functional scales were strongly correlated to each other: ARATvsMAS (0.820, $p=0.004$); ARATvsFMA (0.721, $p=0.019$); MASvsFMA (0.838, $p=0.002$). There was also a strong positive correlation between grip strength and MAS (0.850, $p=0.002$), but not with ARAT or FMA.

Surprisingly, there were no significant correlations between the function of the paretic arm, as assessed by any of the three tests, and brain activity during the imagined or executed movement in either the paretic or the contralateral side or even with BSI.

3.2. Correlations between EEG and fMRI measures

As previously mentioned, all correlations presented in this section have been corrected for patient age, time post stroke and functional assessment score.

Affected hand: motor execution versus motor imagery

Table 2 summarizes the correlations observed between brain symmetry and the activity in the areas of the motor network, at beta and mu frequency during the movement and the imagination of the affected hand.

Table 2: Median (P25;P75) values of brain symmetry index during task of the affected hand (MER or MIR) according to the frequency (beta or mu) and its correlations with activity in ROI.

			Beta Frequency			
Task	BSI		Left Hemisphere	Rho	Right Hemisphere	Rho
Median (P25;P75)						
MER	-0.102 (-0.1545; -0.0185)	+ during task	—	—	↑PrC	0.79
			↑PostC	0.87	↑PostC	0.79
			↑SMA	0.78	↑SMA	0.78
			↑PUT	0.67	—	—
			—	—	↑THAL	0.62
MIR	-0.110 (-0.1674; -0.0200)	+ during task	↑PrC	0.84	↑PrC	0.90
			↑PostC	0.84	↑PostC	0.90
			↑SMA	—	↑SMA	0.90
			↑P1	0.84	—	—
Mu frequency						
Task	BSI		Left Hemisphere	Rho	Right Hemisphere	Rho
Median (P25;P75)						
MER	-0.059 (-0.1489; 0.0143)	+ during task	—	—	—	—
MIR	-0.104 (-0.1409; 0.0007)	+ during task	—	—	↑PrC	0.84

Abbreviations and Symbols: Positive (+) =>increase through contralateral/affected side; increase (↑); decrease (↓) activity; cerebellum (CRBL); motor execution right (MER); motor imagination right (MIR); parietal superior (P1); precentral (PrC); postcentral (PostC); putamen (PUT); supplementary motor area (SMA); thalamus (THAL);

Beta frequency

During MER, the increase in brain asymmetry through the affected side at beta frequency was correlated with an increased activity in contralesional PrC, bilateral SMA and PostC, however it was higher on the PostC left/affected hemisphere. There was also a positive correlation with an increased activity in left PUT and right THAL. During the motor imagery of the affected limb, the

greater the asymmetry through the affected side, the greater activity in bilateral PrC and PostC, contralateral/left P1 and ipsilateral/right SMA, at beta frequency.

Mu frequency

No correlations between real BSI during task were found at mu frequency during the movement of the affected hand. During MIR, the greater the asymmetry through the affected side, the higher the activity in the ipsilateral/right PrC, at mu frequency.

Non-affected hand: motor execution versus motor imagery

Table 3 summarizes the correlations observed between the brain symmetry and the activity in the areas of the motor network, at beta and mu frequency during the movement and the imagination of the unaffected hand.

Table 3: Median (P25;P75) values of brain symmetry index during task of the unaffected hand (MEL or MIL) according to the frequency (beta or mu) and its correlations with activity in ROI.

			Beta Frequency			
Task	BSI		Left Hemisphere	Rho	Right Hemisphere	rho
	Median (P25;P75)					
MEL	0.134 (0.0449; 0.1749)	+ during task	—	—	—	—
MIL	0.129 (0.0485; 0.1471)	+ during task	↓SMA	-0.61	—	—
			—	—	↓P1	-0.59
			Mu Frequency			
Task	BSI		Left Hemisphere	Rho	Right Hemisphere	rho
	Median (P25;P75)					
MEL	0.084 (-0.0195; 0.1686)	+ during task	—	—	↓PrC	-0.72
			—	—	↓PostC	-0.72
MIL	0.092 (-0.0336; 0.1550)	+ during task	—	—	—	—

Abbreviations and Symbols: Positive (+) => contralateral/unaffected side; increase (↑); decrease (↓); cerebellum (CRBL); motor execution left (MEL); motor imagination left (MIL); parietal superior (P1); precentral (PrC); postcentral (PostC); putamen (PUT); supplementary motor area (SMA)

Beta frequency

During the executed movement of the non-affected arm, no correlations existed between real brain asymmetry throughout the task and the activity of any ROI, at beta frequency. Nevertheless,

during MIL, the increased asymmetry through the unaffected side was correlated with a decreased activity in ipsilateral/left SMA and contralateral/right P1.

Mu frequency

During MEL, there was an increased asymmetry through the unaffected side, which was correlated with a decreased activity in contralateral/right PrC and PostC at mu frequency. No correlations were found between the increased asymmetry through the unaffected side at mu frequency during motor imagery of the left hand.

4. Discussion

In the present study, changes in BOLD are indeed associated with changes in BSI and these do not arise from one specific spectral band.

4.1 Age, months post-stroke and baseline assessment correlations with EEG-fMRI

Surprisingly, we did not find any correlation between age and BOLD or BSI changes. This could be explained by lower gray matter perfusion usual in older subjects and discrepancies in neuronal activity response found in different studies related to aging, probably due to baseline cerebral blood flow differences between subjects (De Vis et al., 2015). However, the ischemia can also be an issue.

The greater the number of months post-stroke is, the lower the activation in cerebellum_6 right is during MER, probably due to non-use of the affected hand. Cerebellum is highly interconnected with contralateral primary motor cortex (M1), crucial for the performance and learning of motor skills (Dong, Winstein, Albistegui-DuBois, & Dobkin, 2007; Wang et al., 2010) and, has a important role in hand recovery independently from the degree of cortico spinal tract damage (Rosso et al., 2013). Thus, its recruitment seems to occur in order to compensate M1 lesion (Kaiser et al., 2012; Mintzopoulos, et al., 2009). According to (Wang, et al., 2010), there is an increased activation in cerebellum contralateral to lesion in patients with good recovery during the first six months. The same authors try to explain this with the cerebellum role in motor learning or refer to diaschisis. Contrarily, other researchers mentioned an inverse relationship between activation and functional outcomes seen in several motor areas such as the cerebellum

in a cross-sectional study of chronic patients and/or in a longitudinal study of acute patients (less than 1 year), suggesting that greater activation occurs in patients with greater needs, i.e. severe (Ward, Brown, Thompson, & Frackowiak, 2003a, 2003b). Independently of being severe or mild, stroke patients have abolished or reduced cortico-cerebellar functional connectivity, respectively, and this change in connectivity is associated with poor outcomes (Rosso, et al., 2013). It seems that the density of functional connections in the cerebellum and SMA is correlated with better recovery (Westlake et al., 2012). Seeing that our patients are in a chronic phase and have different degrees of severity, we believe the lack of activity correlated to the months post-stroke is in fact related to lack of movement, experience and/or stimulus. Therefore, cerebellum may also be a target of rehabilitation (Mintzopoulos, et al., 2009), thus, rehabilitation paradigms might be somatosensory-guided learning based (Westlake et al., 2012).

No correlation was found between functional baseline and EEG and BOLD activation, similarly previous studies, with magnetoencephalography, did not find relationships between age and baseline function with imaging measures (Westlake, et al., 2012). Contrarily, (Ward, et al., 2003a) referred to a negative association between functional outcome and degree of a task-related activity. (Kaiser, et al., 2012) also found a relationship between the function and EEG of the affected hand thus, patients with less impairment not only showed higher contralesional event-related synchronization and weaker contralesional event-related desynchronization during ME and MI respectively. Additionally, they considered that greater contralesional activation is associated with poor recovery and higher degrees of stroke impairment. Similarly, Calautti and collaborators (Calautti et al., 2007) stated, the higher activity in contralesional M1 and sensory motor cortex (S1) is, the worse the finger-tapping deficit is, though no such relationship existed for the dorsal premotor cortex and SMA, independently of age and time since stroke. Nonetheless, the main differences obtained can be due to the stroke phase (acute) (Ward, et al., 2003a; Westlake, et al., 2012), or the lack of correction for age and time since stroke (Kaiser, et al., 2012), or even the direct correlation between the task in fMRI paradigm and the BOLD changes and lesion location (Calautti, et al., 2007). These last studies involved patients primarily with left hemiparesis (Calautti, et al., 2007) while ours only had right hemiparesis and conducted different functional outcome measures to correlate.

4.2. Degree of activation in BOLD signal and EEG/ Task-related changes in alpha/beta BSI and BOLD responses: correlation

FMRI and EEG have, as mentioned, differences in terms of spatial and temporal resolution. Previous data suggest that BOLD can be affected by stroke having a delayed response, i.e. prolonged or depressed in patients due to hemodynamic modifications (Carey & Seitz, 2007; Dijkhuizen et al., 2003; Faro & Mohamed, 2006). Seeing that EEG has high time resolution, and beta rhythmic activity constitutes the central drive between the motor cortex and spinal motor neurons (Lopes da Silva, Gonçalves, & De Munck, 2009), the first seconds of each task are the ones that seem to be related with the changes in BOLD signals, as demonstrated in this study.

Different correlations were observed when relating BSI throughout the tasks with the BOLD activity in several brain areas. Similar to a study in healthy subjects (Yuan, et al., 2010), different correlations were also found between alpha/beta BSI and BOLD activity during ME and MI, suggesting that alpha/beta rhythms are functionally coupled with the BOLD signals, possibly over a similar mechanism, not only in sensorimotor areas but also in SMA. The decrease in alpha/beta power may be a result of a decrease in the synchrony of the underlying neural populations and related with increased neuronal activity (Yuan, et al., 2010). Notwithstanding, the main areas, in our data, in which the increased activity was observed, were more contralesional.

This study is in line with the ones from (van Putten & Tavy, 2004), suggesting that un-recovered patients have an increase in brain asymmetry. We demonstrated that patients are more asymmetric through the contralesional hemisphere during tasks. However, those who can increase the asymmetry through the ipsilesional hemisphere during imagination can enhance the activity in the PrC on that side. Despite our patients being asymmetric to the contralesional side during tasks, there is also an increased activation in the ipsilesional hemisphere, suggesting that the assessment with EEG exclusively will fail in terms of the bilateral activity, which usually occurs to help the execution or imagination of the affected hand.

Several correlations were observed, and our data suggests that despite age, time post stroke and severity at beta frequency, when the patients tried to move or imagine their affected hand, an increase in contralesional hemisphere occurred, in particular in PrC, PostC and SMA. This can reflect the dendritic overgrowth due to the overuse of the unaffected hand or the expanded recruitment of the motor networks driven by higher order areas when attempting to execute the

task with the affected hand (Calautti, et al., 2007). The amount of activation in PrC during the learning of movement sequences is correlated with performance achievement (Sosnik, Flash, Sterkin, Hauptmann, & Karni, 2014). Nonetheless, several studies state that an increased activity of the unaffected hemisphere has worse functional results (Rossini, et al., 2003; van Putten & Tavy, 2004). Serrien and colleagues (2004), stated an increase in flow information in contralateral compared to ipsilateral sensorimotor cortex at beta band, in both healthy and well recovered patients, but not in unrecovered ones who had ipsilateral flow. However, when patients performed the task with the affected hand, the information flow from the contralateral was inferior to the ipsilateral hemisphere, contrary to the unaffected hand. Moreover, they found effect at the beta but not at the alpha frequency (Serrien, et al., 2004). Seeing that this study included all types of severity, justifies both the higher correlation with contralateral areas and the correlation with the ipsilateral areas, however a separate analysis was not able to be performed due to the small amount of patients. This cortical ipsilateral activation can be a consequence of the intention or preparation to move the affected hand (Bundy et al., 2012). A similar behavior, i.e. a dominant suppression of alpha and beta power in the contralateral hemisphere, was mentioned during ME or MI of right and left hand in healthy subjects (Yuan, et al., 2010). A negative correlation between BOLD and EEG beta ($r=-0.72$, $p<0.0004$) or EEG alpha ($r=-0.54$, $p<0.005$) contralateral to right hand ROI during imagination and movement tasks was found (Yuan, et al., 2010). The same authors observed a bilateral EEG change during left hand ME and a contralateral during MI, however no correlation was found between EEG changes and BOLD signals. This data suggests that the dominant hand has different activities and strategies compared to the non-dominant hand, justifying our differences between affected and unaffected hand and the lack of correlations in the latter. Alpha and beta desynchronization was previously mentioned to be more lateralized in preparation and bilateral during movement (Platz et al., 2000). The differences to this study can be justified by the use of several etiologies and topographies of cerebral stroke, a wide age difference and mixed hand dominance (Serrien, et al., 2004). Moreover, the EEG data collected separately differ from those during fMRI scanning, even when the signals are recorded under the same external stimulus (Murta, et al., 2015).

Notwithstanding, in this study, the correlations in the contralateral side were higher than the ipsilateral during execution, except for SMA. The similar correlation in SMA during MER can be related to its role in coupling/linking the sensorimotor cortices and the disinhibition of the ipsilateral sensorimotor cortex (Serrien, et al., 2004) however, this did not occur in MIR.

Research highlights the functional connection between SMA and sensorimotor cortex in movement regulation (Serrien, et al., 2004). The SMA manages finger movements since it directly contributes to the cortico-spinal track fibers and seems to be bilaterally more activated in bad recovery (Calautti, et al., 2007). It can also be related to the active concentration of patients in a specific task or to the fact that beta waves are indeed associated with muscle execution over the motor cortex. Nonetheless, the correlation was bilateral and involved a greater area at beta band. Hence, SMA region is involved in coordinating temporal sequences of actions and the formation of sequential procedural memory, thus the finger-thumb sequence highly activating it. Furthermore, the SMA role in MI can involve the suppression of M1 (Halder et al., 2011). The SMA recruitment in chronic stroke patients, helps the affected M1 (Mintzopoulos, et al., 2009), not only during execution but also imagination. An overall hyper activation in the early phase of reorganization in some areas, such as SMA, was observed during active and passive movement (Tombari et al., 2004). Even associated to muscle contractions, a strong correlation still at beta band during MIR. The beta activity normally increases during tiredness, light sleep and with mental activation (Tatum, 2008), thus justifying the above correlation since MI is an internal rehearsal of ME and a mental process. Nonetheless, this can be a compensating strategy or a maladaptive plasticity.

The correlation observed during MIR in ipsilesional parietal superior could be justified by its role not only in spatial attention, spatial awareness and sensory integration but also in movement intention/planning, decision-making and ideation (Andersen & Cui, 2009; Sirigu, et al., 1996) which is more predominantly on the left, and can be useful in rehabilitation with a brain-computer interface (Andersen & Cui, 2009; Mizuguchi, Nakata, & Kanosue, 2014). MI demands more attention compared to execution, justifying the lack of correlation during MER. However, during the imagination of the unaffected hand, the opposite occurs probably due to the establishment of the motor schema since MI is no longer a novelty (Xie, Xu, Long, Yao, & Wu, 2015), and the amount of brain activity is dependent on imagined force levels (Mizuguchi, et al., 2014).

Similarly to what was cited in healthy subjects (Yuan, et al., 2010), no correlations were found between EEG changes and BOLD signals during ME of the non-dominant hand at beta frequency. Contrarily, the correlations found in the present study in MI suggests that it can be due to use-dependent/experience neuroplasticity in stroke patients and that the paradigm is no longer a complex one, so it does not demand much more bilateral activation (Takeuchi, Oouchida, &

Izumi, 2012). Seeing that patients needed to use the unaffected hand daily, they were able to perform the movement effortlessly, possibly due to the development of representations in particular brain areas that produced the same behavior with higher neural efficiency, justifying the lack of correlations during MEL at beta frequency. As described, it is not a question of the amount of practice but the performance gains, which interfere in the activation (Sosnik, et al., 2014). It seems that stroke patients have different strategies, i.e. areas activated if the movement is performed with the affected or with the unaffected hand. Notwithstanding, the ipsilesional/"unaffected" hand tends to be slower and less "coordinated" following left hemisphere damage (Schaefer, Haaland, & Sainburg, 2009). In addition, this study also shows less non-primary motor areas correlated to the unaffected compared to affected hand movement execution. The negative correlations observed at mu frequency in PrC and PostC are related with mu role in inhibition of cortical areas, as expected (Brinkman, et al., 2014).

Likewise to other studies, a higher imagery task demand implies an increase in alpha power in ipsilateral sensorimotor cortex (Brinkman, et al., 2014). We found a correlation between the contralateral hemisphere BSI and the increased activity in ipsilateral PrC, during MIR at mu frequency, this can be the result that the ipsilateral motor processing involved motor planning and selection of the movement rather than the ME in itself (Wisneski et al., 2008). Contrarily, the decrease in power at beta frequency in the contralateral sensorimotor mentioned by the same authors was not conferred in this study.

Recovery depends on the reorganization of the activity in both hemispheres, therefore with improvement, the activations that are initially lateralized towards the ipsilateral cortex can shift back to the contralateral cortex (Westlake, et al., 2012). Future work may extend these findings to the effect of intervention in chronic stroke patients.

The small size of our subject cohort as well as the heterogeneity of our sample in times post stroke may have limited our results. However, we attempted to use an ideal paradigm, in particular the finger–thumb-tapping task that enables the determination of the motor recovery degree (Nelles, 2004) and demonstrates function in the PrC gyrus area in 89% of stroke patients (Faro & Mohamed, 2006). We also combined it to MI, which seemed to be preserved in stroke patients independently of the functional deficits, becoming a more complete paradigm. Despite the heterogeneity in time post-stroke, all patients were in the chronic phase, but stable in terms of neuroplasticity compared to the acute phase. Nevertheless, all the correlation analyses were

controlled to age, time-post stroke and baseline function. However, to validate these findings, a replication in a bigger sample is desirable. It is promising that, even in the presence of this heterogeneity, we found a consistent relationship between BOLD and BSI changes.

5. Conclusion

Our study showed that an EEG-fMRI relationship in chronic stroke patients did not derive from one specific spectral band. The correlation analyses demonstrated that changes in activation patterns were related to BSI alterations and different from the affected compared to unaffected hand movement as well as during execution compared with imagination.

6. References

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**Physiotherapy based on problem-solving in upper limb function
and neuroplasticity in chronic stroke patients: a case series**

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ABSTRACT

RATIONALE, AIMS, AND OBJECTIVES: Upper limb recovery is one of the main concerns of stroke neurorehabilitation. Neuroplasticity might underlie such recovery, particularly in the chronic phase. The purpose of this study was to assess the effect of physiotherapy based on problem-solving in recovering arm function in chronic stroke patients and explore its neuroplastic changes.

METHODS: A small sample research design with a n of 3 using a pre-post test design was carried out. Neuroplasticity and function were assessed by using fMRI (during motor imagery and performance), action research arm test, motor assessment scale and Fugl-Meyer assessment scale, at three sequential time periods: baseline(m0–before a 4-week period without physiotherapy), pre-treatment(m1) and post-treatment(m2). Minimal clinical important differences and a recovery score were assessed. Assessors were blinded to moment assignment. Patients (3) underwent physiotherapy sessions, 50min, 5 days/ week for four weeks. Four control subjects, served as a reference for fMRI changes.

RESULTS: All patients recovered more than 20% after intervention. Stroke patients had similar increased areas as healthy subjects during motor execution but not during imagination at baseline. Consequently, all patients increased activity in the contralateral precentral area after intervention.

CONCLUSIONS: This study indicates that four weeks of physiotherapy promoted the recovery of arm function and neuroplasticity in all chronic stroke patients. Future research is recommended to determine the efficacy of this therapy.

Keywords: Arm; Bobath Concept; Neuroplasticity; Physiotherapy; Rehabilitation; Stroke

INTRODUCTION

Upper limb function is affected in a great percentage of stroke patients however, only a small fraction achieves complete recovery(Kwakkel, Kollen, van der Grond, & Prevo, 2003; Williams, Galea, & Winter, 2001). Thus, recovery is a priority of neurorehabilitation(Hara, 2015).

Rehabilitation and recovery after stroke is directed by neuroplasticity(Hara, 2015) i.e., the ability of the brain to change its structure and function(Graham, Eustace, Brock, Swain, & Irwin-Carruthers, 2009). Most importantly, a limited capacity for neuroplasticity in the non-stimulated brain means, patients sustain functional deficits throughout life(Taupin, 2006). Despite being faster and more evident in the first months(Taupin, 2006), the potential for neuroplasticity change and adaptation continues in the chronic period after the event thus harnessed by different interventions(Hara, 2015; Hodics, Cohen, & Cramer, 2006). Besides this acute/chronic distinction with ill-defined limits, the ability to promote neuroplasticity also depends on intervention type, age, lesion location (cortical/subcortical or dominant/non dominant hemisphere) and handedness(Carey & Seitz, 2007; Ward, Swayne, & Newton, 2008; Zemke, Heagerty, Lee, & Cramer, 2003). Hence, there are many techniques, such as functional magnetic resonance imaging (fMRI), which researchers use to probe brain activity as well as the impact of neurorehabilitation strategies upon neuroplasticity. In this regard, FMRI is crucial since it has high spatial resolution, thus providing insights concerning the brain reorganization phenomena underlying functional recovery after neurorehabilitation(Hodics, et al., 2006).

Motor rehabilitation traditionally focuses on conventional therapy, the most widespread being physiotherapy based on the Bobath Concept approach (PT)(Graham, et al., 2009; Kollen et al., 2009; Luke, Dodd, & Brock, 2004b; Tyson, Connell, Busse, & Lennon, 2009; Vaughan-Graham, Cott, & Wright, 2015a). It attempts to integrate postural control and task performance with a specific focus on the quality of the latter, thus enhancing movement efficiency and quality(Vaughan-Graham & Cott, 2016). In practice, the key aspects of the Bobath clinical framework are the analysis of task performance, the relationship of posture and movement, and the role of sensory information in motor control(Vaughan-Graham & Cott, 2016). This approach focuses on neurophysiologic and motor learning theories which detect and analyze problems within functional activities and daily life participation(Kollen, et al., 2009), and assess movement components and primary impairments, improving efficiency and promoting a generalization in daily life(Graham, et al., 2009). Repetition, functional goal-directed activities and increased

attention during learning are common strategies and can induce changes in cortical representation, hence neuroplasticity, which is use-dependent(Arya, Pandian, Verma, & Garg, 2011; Graham, et al., 2009).

Despite these indicators and three systematic reviews(Kollen, et al., 2009; Luke, et al., 2004b; Paci, 2003), pointing to the effectiveness of this therapy, it is still controversial, particularly when considering data which reveals no effects of such intervention(Paci, 2003). These discrepancies can be due to the use of inappropriate outcome measures when assessing the improvement at motor level(Levin & Panturin, 2011) or due to the intervention procedures which do not reflect the current practice(Vaughan-Graham, et al., 2015a). Indeed, recent studies reveal that this approach has a similar efficacy compared to a Constraint-Induced Therapy in patients with high functional levels(Huseyinsinoglu, Ozdincler, & Krespi, 2012) while several others state the Bobath concept to be more effective than other therapeutic approaches(reviewed in Vaughan-Graham, Cott, & Wright, 2015b). Nonetheless, PT is more inclusive and therefore can be applied to any patient no matter age or degree of functional severity(Graham, et al., 2009),(Vaughan-Graham, et al., 2015a).

Consequently, this case series assessed the effect/impact of PT on the recovery of upper limb function in chronic stroke patients and explored its neuroplasticity changes.

MATERIAL AND METHODS

Type of study

A small sample research design with a n of 3 using a pre-post test design was used.

Sample and setting

Patients were recruited from the outpatient service at a Regional General Hospital after the Ethics Committee approved protocol. Patients with a first-ever left middle cerebral artery (MCA) episode, cortical infarcts ≥ 12 months, were prospectively selected. Infarct site was identified using structural MR or CT scans and classified through clinic radiological criteria. Exclusion criteria involved: hand plegia, persistent language and cognitive deficit (Mini Mental State Examination), major sensory deficits, inattention, visual impairment, depression, inability to toilet oneself independently prior to stroke, left-handedness (Edinburgh Handedness Inventory), severe spasticity (Modified Ashworth Spasticity Scale ≥ 3)(Page, Levine, & Khoury, 2009), inability to

perform accurate motor imagery, i.e., a score below 75% in the hand rotation component (see Sharma et al., 2009), and contraindications to MRI (e.g. claustrophobia or pacemaker).

Four control subjects (2 males) were recruited through local advertisement to serve as a reference of fMRI changes and matched to cases regarding age, gender and education. Additionally, control subjects had no history of medical disorders.

All subjects gave written consent according to the Declaration of Helsinki.

No dropouts or unpleasant experiences occurred with any assessment or therapy.

Procedures

Each patient was assessed at three sequential time periods: 5 weeks before intervention (baseline (m0) - no PT administered); one week before initiating intervention (pre-treatment (m1)) to evaluate spontaneous recovery by time and to ensure stable baseline (control condition) and finally, one week after intervention (post-treatment (m2) - experimental condition), with a 4-week interval between each assessment.

Healthy subject outcomes were recorded at baseline and after a 4-week interval (m0 and m1, respectively).

Motor execution and Imagination Paradigm for fMRI

fMRI assessed neuroplasticity (cortical activity and change of activation patterns) as a primary outcome measure. The fMRI paradigm, which was repeated five times, is a block design finger–thumb opposition sequence (30seconds each), alternating motor imagery or motor execution (MI or ME) with a rest for each hand. The initiating hand was random (MI_right/rest/ME_right/rest/MI_left/rest/ME_left/rest or MI_left/rest/ME_left/rest/MI_right/rest/ME_right/rest) and finger movements during scanning were monitored by using individual cameras and then registered based on the EMG.

fMRI data acquisition and processing

Setting: Siemens 3.0T (Siemens, Magnetom Vision, Erlangen, Germany), FoV: 245mm², spatial resolution: 3x3x3mm³, TR 3s, TE 30ms, Flip Angle: 90°, 46 slices. fMRI analysis was processed in Statistical Parametric Mapping software (SPM8 -<http://www.fil.ion.ucl.ac.uk/spm/>) using a standard pre-processing pipeline (slice timing correction, realignment, coregistration of structural and functional images, normalization and smoothing). Excessive head movement did not occur. Additionally, T1-weighted anatomical images with pulse sequence parameters of the entire brain were obtained: FoV 256 mm²; spatial resolution: 1x1x1.2mm³; TR=2300ms; TE=2.98 ms; flip angle 9°; 160 slices.

Behavioral Measure

Motor impairment level and upper limb function were assessed by Action research arm test (ARAT), Fugl-Meyer assessment scale – arm section (FMA) and Motor assessment scale (MAS)(Carr, Shepherd, Nordholm, & Lynne, 1985; Page, Fulk, & Boyne, 2012; Yozbatiran, Der-Yeghiaian, & Cramer, 2008). The modified Rankin Scale (mRS) was used to measure the global/overall degree of disability/dependence. Each clinical score demonstrates good to excellent intrarrater variability, reliability, all valid in a stroke population(Croarkin, Danoff, & Barnes, 2004). Assessment was performed and documented on video while two assessors (blind for assessment moment) scored behavioral outcome measures based on videotaped information at the end.

Intervention

Physiotherapy based on the Bobath concept

This approach usually takes 2-20 weeks(Kollen, et al., 2009; Luke, Dodd, & Brock, 2004a; Paci, 2003), in a mean of 40min/day during 20-24 sessions. Nonetheless, due to time management/efficiency, PT involved 20 sessions of 50min, 5 days/week(Luke, et al., 2004a; Wang, Chen, Chen, & Yang, 2005), during 4 weeks(Paci, 2003; Wang, et al., 2005). The therapist who performed all treatments had more than ten years of experience in this therapy and has one basic course, two advanced courses and several other thematic courses. The interventions were grouped in 5 major items: facilitated movement; mobilization; practicing an activity component and/or whole task and teaching patients (see Tyson, et al., 2009). All interventions, individually programmed, aimed at improving postural control of trunk and shoulder girdle enabling more selective arm movement and increasing strength and function(Vaughan-Graham, Cott, & Wright, 2014), to recover full motor range patterns, in order to enhance efficiency and maximize function and reducing the severity of impairments where they influence function(Levin & Panturin, 2011). Tasks were previously known, simple with a functional goal not resembling the outcome measures i.e tasks involved the facilitation of sitting to standing and/or walking, scapulohumeral rhythm, reaching patterns, preparing for upper limb placing, selective strength training of the intrinsic muscles of the hand, among others(Raine, Meadows, & Lynch-Ellerington, 2009). All interventions were administered at the patients' homes.

Data Analysis

Behavioral data, due to sample size, was analyzed based on the minimal clinical important difference (MCID), representing the smallest amount of change in an outcome, which may be important to the patient or therapist. The MCID was set at 10% of the total range of the scales, except for FMA (scores between 4.25 and 7.25), based on previous studies and together with the patients (Chen, Chen, Hsueh, Huang, & Hsieh, 2009; Page, et al., 2012; Yozbatiran, et al., 2008). In order to account for the functional heterogeneity of patients at baseline, a recovery score for the behavioral outcome was calculated, i.e., the sum of the differences between m1 and m2 for each score, divided by the total score at m1 (i.e. the sum of all measures) (e.g. $((FMA_{m2}-FMA_{m1})+(ARAT_{m2}-ARAT_{m1}))+(MAS_{m2}-MAS_{m1})) / (FMA_{m1}+ARAT_{m1}+MAS_{m1})$) (Westlake et al., 2012). Based on the directionality of the changed scores, increased scores represented an improvement in all clinical tests.

Regarding the fMRI data, statistical analysis was performed using SPM8. For the first-level analysis, five conditions were modeled, namely rest periods, movement execution for right/affected (MER) and left/unaffected hands (MEL), movement imagination for right/affected (MIR) and left/unaffected hands (MIL) with 30second duration. For this study, only contrasts representing ME and MI of the affected hand were considered (i.e. MIR, MER), by contrasting the corresponding conditions with baseline condition. The regions of interest were based on the bilateral ME network: precentral and postcentral, supplementary motor area (SMA), parietal superior, paracentral, thalamus, putamen, pallidum and cerebellum. The contrast estimate presented has a T/F-Stat threshold of $p < 0.001$ combined with a minimum/critical cluster size of 20 voxels. These regions were defined by using the Automated Anatomic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). The data is presented in reference to the side of cortical activity, using the terms contralateral/left or ipsilateral/right for all participants, which in stroke patients refers to left/ipsilesional or right/contralesional cortex, respectively.

The differences between contrast estimate at different moments were also calculated subtracting the activation areas from m1 and m0 and between m2 and m1, with a T/F-Stat threshold of $p < 0.001$, without a minimum cluster size.

RESULTS

Case description

Table 1 shows the main subject characteristics.

Table 1: Patient characteristics according to age, gender, living situation, educational level and cognitive level, comorbidity, lesion location, time post stroke and severity

Group		Age (years)	Gender (M/F)	Living situation	Educational level (years)	MMSE	Comorbidity	Lesion Site	Time from stroke (months)	mRS x/6
Stroke	P1	72	M	with family	4	27	—	L MCA	14	3
	P2	61	F	alone	4	29	Knee arthrosis	L MCA	37	4
	P3	43	F	with family	12	28	—	L MCA	18	2
Healthy	C1	66	M	with family	4	29	—	—	—	—
	C2	74	M	with family	4	28	—	—	—	—
	C3	63	F	alone	7	28	Knee arthrosis	—	—	—
	C4	48	F	with family	9	30	—	—	—	—

Three stroke patients were recruited aging from 43 to 72, (1 male) with time from stroke onset ranged from 14 months to 37 months, and four healthy control subjects (2 males), aging from 48 to 74 (Table 1). The patients could walk outdoors (however P2 needed to use a cane for 10 meters distance), had familiar support and were retired since stroke, due to their incapacity to do the usual tasks.

Clinical and Functional Recovery

Table 2 describes the MCID reference values of each functional assessment, baseline values and gains after 4-weeks without any intervention ($m1-m0$), after 4-weeks of PT ($m2-m1$) i.e. differences between each scale total score at $m1$ and $m0$ and $m2$ and $m1$, respectively, and the total recovery score.

Table 2: Functional outcome measures and respectively minimal clinically important differences (ARAT, MAS and FMA) of each patient, differences/gains after 4 weeks without intervention (m1-m0), with physiotherapy (m2-m1) and respectively recovery score.

Outcomes and MCID reference value/ Total scale value	Moment	P1	P2	P3
ARAT 5.7($\pm$ 2sd) points /57 total	Baseline	29	4	48
	m1-m0	3	4	-5
	m2-m1	1	-1	8*
MAS 1.8 points/18 total	Baseline	6	2	12
	m1-m0	2.5*	-1	1.5
	m2-m1	2*	1	3*
FMA 4.25 to 7.25 points/66 total	Baseline	18	14	43
	m1-m0	6*	-5	-6
	m2-m1	12*	8*	6*
Total Recovery Score (%)	m1	22*	-1	-8
	m2	27*	41*	20*

* Higher than MCID

ARAT - Action research arm test; FMA - Fugl-Meyer assessment scale – arm section; MAS - Motor assessment scale; MCID- Minimal Clinically Important Difference; m1 – moment 1 after 4-weeks without any intervention; m1-m0 – gains after 4-weeks without any intervention; m2 – moment 2 after 4-weeks of intervention; m2-m1 - gains after 4-weeks of intervention

During the non-intervention period, the female subjects (P2 and P3) exhibited stable or even decreased motor deficits, i.e., below MCID. P1 improved MAS and FMA and kept improving after intervention (Table 2).. After 4-weeks of PT, P1 showed improvement in two of three outcome measures, P2 only improved in FMA while P3 improved in all measures, being FMA the most significant for all patients (Table 2). The recovery score was higher after four weeks of intervention even in P1.

FMRI Findings

This section presents the main fMRI findings, which occurred cortically, ipsilateral/right and/or contralateral/left to the hand movement or imagination.

Healthy and non-intervention stroke patient motor execution

Table 3 depicts the areas where increased activity was observed, during ME of the right hand in comparison to rest, in healthy subjects (+) and stroke patients (x), at baseline, after a four-week-interval and post-intervention.

Table 3: Motor execution activity compared to rest in healthy subjects and stroke patients at different moments (m0, m1 and m2)

Region	Side	m0							m1							m2		
		C	C	C	C	P	P	P	C	C	C	C	P	P	P	P	P	P
		1	2	3	4	1	2	3	1	2	3	4	1	2	3	1	2	3
Precentral	C	+	+	+	+	x	x	x	+	+	+	+	x	x	x	x	x	x
Precentral	I	+	+	+	+		x	x	+	+		+	x	x	x		x	x
Postcentral	C	+	+	+	+	x	x	x	+	+	+	+	x	x	x		x	x
Postcentral	I	+	+		+		x	x	+	+		+	x	x	x		x	x
SMA	C	+	+	+	+		x	x	+	+	+	+		x	x		x	x
SMA	I	+	+		+		x	x	+	+				x	x		x	x
Parietal superior	C	+						x	+					x	x		x	x
Parietal superior	I	+						x	+				x	x			x	
Paracentral	C		+			x				+					x			
Paracentral	I																	
Cerebellum_6	C	+	+		+	x	x	x	+	+	+	+		x	x		x	x
Cerebellum_6	I	+	+	+	+	x	x	x	+	+	+	+		x	x		x	x
Cerebellum_8	C					x	x	x							x		x	x
Cerebellum_8	I	+	+		+	x	x	x	+	+		+			x		x	x
Thalamus	C		+	+	+		x	x		+			x	x			x	x
Thalamus	I		+				x		+	+			x	x			x	x
Putamen	C				+		x			+			x	x			x	x
Putamen	I						x		+				x	x			x	x
Pallidum	C				+		x				+							x
Pallidum	I				+													x

+ or x- increased activation during right hand execution compared to rest, in healthy subjects or patients, respectively in the different moments (m0- baseline; m1 - 4/wk interval/pre-intervention; m2-post-intervention), with a T/F-Stat threshold of $p < 0.001$ (minimum cluster size of 20 voxels)

I = ipsilateral; C = contralateral.

At baseline (m0) all healthy subjects showed increased activity in bilateral precentral. Moreover, increased activity in bilateral postcentral, SMA and cerebellum_6 and right cerebellum_8 was also observed, except in C3. P2 and P3 had the same behavior at baseline in precentral, postcentral, SMA and cerebellum_6, however the activity in cerebellum_8 was bilateral. C1 also increased activity in the bilateral parietal superior area. C3 as well as P1 demonstrated more contralateral cortical activity. The activation in basal ganglia was more variable.

After a four-week-interval, the areas where increased activation was observed in healthy subjects, remained similar however, with some differences in terms of intensity of contrast estimate and

volumes. In general, healthy subjects, 3 out of 4 increased their contrast estimate intensity (except for C4). All healthy subjects increased left precentral area activity however, while men increased volume/area, women decreased, i.e., focused activation. The augmented activation from the ipsilateral cerebellum 6 and contralateral postcentral areas was observed in 3 out 4 healthy subjects, i.e., despite the increased activity of left precentral area, women also increased activity in both right cerebellum 6 and 8 (C3) and left postcentral (C4). Notwithstanding, there was decreased activity from m0 to m1 in all areas at m0 in both C3 and C4. However, men had different behavior, not only compared to women but also between them; C1 increased activity while C2 decreased. Both C1 and C2 increased bilateral postcentral, right cerebellum 6 and left putamen but C2 decreased activity in left cerebellum 6, right thalamus and bilateral paracentral. Thus, a quite heterogenous pattern.

Similar to healthy subjects, P1 increased brain activity intensity between m0 and m1. Contrarily, P2 and P3 decreased it. No differences between moments were found during a four-week-interval without intervention (m1-m0) in contralateral precentral area however, all patients presented increased activity in other areas such as, postcentral (P1 bilateral while P2 and P3 contralateral) and parietal superior (P1 contralateral while P2 and P3 bilateral). P1 also increased activity in bilateral thalamus and putamen while P2 increased in right thalamus and cerebellum_8. Like healthy subjects, P1 increased while P2 and P3 decreased volume/area.

There was decreased activity in all patients in postcentral (P1 contralateral while P2 and P3 bilateral), SMA (P1 and P2 contralateral while P3 ipsilateral), cerebellum_6 (P1 contralateral while P2 and P3 bilateral) and cerebellum_8 (P1 and P2 bilateral while P3 contralateral). Moreover, there was also decreased activity in the contralateral and bilateral precentral areas, in P2 and P3 respectively.

Healthy and non-intervention stroke patient motor imagination

Table 4 illustrates the areas where increased activity was observed, during motor imagination of right hand in comparison to rest, in healthy subjects (+) and stroke patients (x) according to the moment.

Table 4: Motor imagination activity compared to rest in healthy subjects and stroke patients at different moments (m0, m1 and m2)

Region	Side	m0							m1							m2		
		C 1	C 2	C 3	C 4	P 1	P 2	P 3	C 1	C 2	C 3	C 4	P 1	P 2	P 3	P 1	P 2	P 3
Precentral	C	+	+	+	+			x	+	+	+	+			x			
Precentral	I	+	+	+	+			x	+	+	+	+			x			x
Postcentral	C	+	+		+				+	+	+	+			x			
Postcentral	I	+	+		+				+			+			x			
SMA	C	+	+	+	+			x	+	+	+	+			x			
SMA	I	+	+	+	+			x	+	+	+	+			x			
Parietal superior	C		+	+	+				+		+	+		x			x	
Parietal superior	I		+	+					+	+	+						x	
Paracentral	C																	
Paracentral	I																	
Cerebellum_6	C		+	+	+						+	+			x			
Cerebellum_6	I		+	+	+						+	+			x			
Cerebellum_8	C																	
Cerebellum_8	I		+	+							+							
Thalamus	C		+	+	+						+	+					x	
Thalamus	I		+								+							
Putamen	C		+	+							+							
Putamen	I																	
Pallidum	C			+							+							
Pallidum	I			+							+							

+ or x - increased activation during right hand imagination compared to rest, in healthy subjects or patients, respectively in the different moments (m0- baseline; m1 pre-intervention; m2-post-intervention), with a T/F-Stat threshold of $p < 0.001$ (minimum cluster size of 20 voxels). I = ipsilateral; C = contralateral.

In healthy subjects, similarly to ME, all subjects showed, at baseline (m0), increased activity in bilateral precentral and SMA, and except for C3, an increased activity in bilateral postcentral was observed. Three of four subjects (i.e. except C1) showed increased activity in bilateral cerebellum_6, in parietal superior (C2 and C3-bilateral or C4-contralateral) and in thalamus (C2 bilateral and C3 and C4 contralateral). Comparing to MER at baseline, intensity was relatively lower during MIR except for C2, who had quite similar behavior, not only in intensity but also in regions.

At baseline, two out of three patients were unable to increase activity comparatively with rest at baseline (P1 and P2), while P3 increased bilateral activity in the precentral and SMA areas.

All healthy subjects exhibited increased activity in the bilateral precentral area after a four-week interval. However, the behavior was very different in each subject in the remaining areas, not only in which specific areas and tendency (increase or decrease) but also in intensity (preserved, decreased or increased). C1 only increased activity (despite the mentioned area also increasing in the bilateral postcentral and parietal superior and ipsilateral SMA). C2 decreased activity and intensity in all the areas he had previously increased at m0. Both C3 and C4 decreased in contralateral SMA, however C3 also decreased in contralateral precentral and right cerebellum_6. Besides, there was increased activity in bilateral parietal superior and cerebellum_6 in subject C3 and, in contralateral postcentral and cerebellum_6 in subject C4. Comparing to baseline, C3 and C4 increased contrast estimate intensity.

After reassessment, P1 maintained the tendency at m0, but P2 was able to increase activity in contralateral/ipsilesional parietal superior. Moreover, owing to the reduction in volume/area, P3 increased activity in bilateral precentral and cerebellum_6, and in contralateral/ipsilesional postcentral but decreased in contralateral/ipsilesional precentral.

Effect of physiotherapy on stroke patients

After a four-week intervention period, all patients increased contralateral/ipsilesional precentral activity during ME. Besides this, P2 and P3 increased activity in the ipsilateral/contralesional precentral and in bilateral postcentral areas, cerebellum_6 and 8, putamen, pallidum and thalamus. P2 also increased activity in bilateral parietal superior areas. Relating to intensity, P1 maintained the same when comparing the differences between moments, while P2 and P3 increased more than double. There was a decreased activity in postcentral in all patients (P1 and P3 bilateral, P2 ipsilateral), in bilateral parietal superior (P2 and P3) and in bilateral SMA (P3).

During imagination, behavior was totally different among subjects, for P1 there was no change in the brain activity comparing to rest, P2 increased in contralateral/ipsilesional parietal superior and SMA while P3 increased the ipsilateral/contralesional precentral area, and decreased bilateral precentral, postcentral and cerebellum_6 comparing to m1.

DISCUSSION

The present paper, a pre post-test small sample research design ($n=3$), was conducted to assess the impact of Bobath concept on motor network plasticity in patients with chronic cortical left MCA stroke. Notwithstanding our small sample size, patients showed an improvement greater than the minimal clinically important difference and in the total recovery score after intervention, suggesting the benefit of intervention. Despite the different outcome measures used, functional gains are consistent with other studies(Huseyinsinoglu, et al., 2012; Langhammer & Stanghelle, 2011), i.e., intervention based on Bobath concept improves at least one functional measure(Huseyinsinoglu, et al., 2012; Langhammer & Stanghelle, 2011;Timmermans AA et al., 2013). This is striking, considering these chronic patients for whom spontaneous recovery is minimal(Taupin, 2006), obtained results within a relatively short timeframe of 4 weeks(Page, Szaflarski, Eliassen, Pan, & Cramer, 2009). Thus, the data suggests motor deficits in such patients are amenable to PT suggesting more prolonged intervention may in fact induce greater recovery.

Interestingly, even with chronic stroke, two out of three patients (P2 and P3) had a worsening of their upper limb function during the period of non-intervention. Although P1 improved, the recovery score was even higher after intervention (22% comparing with 27%), and when considering FMA, the result doubled in the same period.

Regarding fMRI findings, in healthy subjects, similarly to other studies, imagined or executed movements have the participation of the same cortical areas(Butler & Page, 2006; Page, Levine, & Leonard, 2007; Seitz, Matyas, & Carey, 2008; Weiss et al., 1994), with additional increased activity in precentral and postcentral areas(Hanakawa, Dimyan, & Hallett, 2008; Jeannerod, 1995; Lacourse, Orr, Cramer, & Cohen, 2005; Weiss, et al., 1994) yet, the magnitude and volume of brain activation is more limited during MIR compared to MER, in healthy subjects(Sharma, et al., 2009). The ipsilateral hemisphere (primary motor cortex (M1), premotor area, primary sensory cortex and SMA) and bilateral cerebellar activation during performance of complex movement, was previously mentioned in healthy subjects(Park et al., 2008), which is consistent with our results. Consequently, the recruitment of several secondary areas in both healthy subjects and patients during MER and MIR can be related to the task itself. The increased activity in SMA comparably to rest, not only during MER but also during MIR, can be related to its

facilitation effect in distal muscles(Ward, 2011), i.e., it seems to be also guided throughout the task.

Stroke patients have similar behavior to healthy subjects at baseline, in contralateral/ipsilesional precentral and post central area and ipsilateral/contralesional cerebellum, during MER but quite different during MIR. In patients, the bilateral activation was quoted as a recruitment of the unaffected hemisphere to complete the task(Butler & Page, 2006). Nonetheless, our data suggests that patients with cortical stroke, had different abilities to perform motor imagination compared to healthy volunteers, since stroke may have damaged the intra-cortical circuitry, affecting cortical reorganization to compensate for functional deficits(Luft et al., 2004). Although MI ability was assessed in all patients, age may have interfered. Indeed, the ability to mentally simulate upper-limb movements has been shown to decline with age(Saimpont, Pozzo, & Papaxanthis, 2009), justifying differences between the inability of P1 and ability of P3 to perform MI. However, according to gender, the results were unexpected, since males seem to facilitate MI, possibly due to gender differences in visuospatial/visuomotor processing(Schaechter & Perdue, 2008; Schuster et al., 2011), suggesting age having greater impact on MI ability.

After a four-week interval, healthy subjects kept increasing activity in contralateral precentral compared to m0. Though our patients were not successful in this initial period, they were after a four-week intervention. The fact that there is less task related contralateral/ipsilesional activity during a non-intervention period, and increased after intervention, compared to baseline, was previously discussed, in patients with greater impairment(Ward, 2011). The decrease in cortical activation induced by ME between first (m0) and second (m1) assessments likely reflects a test-retest effect, probably due to task learning(Rossini et al., 2007) or training(Dong, Winstein, Albistegui-DuBois, & Dobkin, 2007). Nonetheless, our results during ME had a different magnitude (lower contrast estimate intensity) in patients compared to controls, suggesting its mechanisms (i.e. susceptibility to training/motor learning) can be affected in such patients.

A previous study revealed similar decreases in brain activation across multiple scan sessions, but only in recent patients and not controls(Ward, Brown, Thompson, & Frackowiak, 2003a), signifying overactivation in primary and secondary motor areas at baseline(Ward, Brown, Thompson, & Frackowiak, 2003b), which seems to be present in the chronic phase. Two different patterns of brain activation changed i.e., increased or decreased volume and the

uniform or mixed patterns was previously mentioned in stroke patients, after intervention(Pundik et al., 2015), similar to what occurred in this study.

The above-mentioned and our results suggest that P1 probably performed some tasks (beyond physiotherapy) during the non-intervention period. The reduction in areas at m2 focusing on precentral area, could be related to the improvement, similar to pruning during neurodevelopment(Ward, 2011), although the opposite occurred in P2 and P3, which might be characteristic of cortical stroke patients or gender.

Well-recovered hand function relying mostly on ipsilesional/contralateral activity, is generally accepted(Calautti & Baron, 2003), therefore, the increase in contralateral/ipsilesional precentral area could justify the augmented function in P2 and P3 at m2 and the higher increase in P1. Nonetheless, some controversy exists regarding the role of contralateral/ipsilesional M1, the current deficit and patient improvement. Some authors have mentioned that recruiting contralateral/ipsilesional M1 differs across patients in a way largely independent to the baseline function or deficit(Calautti & Baron, 2003). While, more recently, others refer there are differences in fMRI changes regarding severity at baseline, i.e., a decrease or increase in brain activation occurs according to better or worse motor function for proximal arm at baseline respectively, especially in contralateral M1 and ipsilateral SMA which is independent of functional improvement(Pundik, et al., 2015). This suggest that the variability in our results was the consequence of our patient characteristics, i.e., none had language or cognitive deficits needed to understand instructions; the severity at baseline, since some studies mentioned the strategy to recovery is different and age. An increase in contralateral/ipsilesional or decrease/contralesional in ipsilateral hemisphere seems to be different strategies to improve function.

The remaining bilateral increased and decreased activity observed in P2 and P3 could be justified by “new” closed-loop circuit between the cerebellum and the postcentral area, because the somatosensory cortex (located in the postcentral area) contributes to the corticospinal tract(Caligiore et al., 2017). Since SMA seems to be bilaterally more activated in bad-recoverees so it can be the necessary strategy to induce higher post-treatment function in severe patients. The decreased activation in P3 can be related to her recovery, since SMA activity seems to be a compensation to assist M1(Mintzopoulos et al., 2009).

Both P2 and P3 increased ipsilateral activity, previously correlated with poor outcome in subcortical stroke(Calautti & Baron, 2003), however since both patients improved upper limb function, this can be related to the use of the unaffected hemisphere, especially ipsilateral/contralesional premotor cortex because it has a potential and essential role in post-stroke rehabilitation(Calautti & Baron, 2003; Ward, 2011). Hence, the ipsilateral/contralesional hemisphere activation observed in our study could be related to a new functional architecture of the brain after cortical stroke. This new motor system reorganization may not be as effective as an undamaged brain but an alternative to producing a more effective movement, in these particular cases, more function. However, this can also be observed after normal ageing, i.e. a recruitment of additional areas, in particular in the ipsilateral/contralesional hemisphere(Ward, 2011), justifying the similar results in healthy subjects. The success of recovery in chronic patients involved the recruitment of alternative single or multiple functional brain regions in contralateral/ipsilesional and ipsilateral/contralesional hemispheres(Pundik, et al., 2015).

It has been shown that stroke patients with lesions of the precentral cortex, such as the ones in the present study, have increased connectivity between the cerebellum and intact perilesional areas(Mintzopoulos, et al., 2009) and that a synergistic action of both regions is essential for the performance and learning of motor skills(Dong, et al., 2007). More importantly, recovery of hand function after acute stroke has been directly correlated with increased activation of the ipsilateral cerebellum, and not with any other area(Rosso et al., 2013; Small, Hlustik, Noll, Genovese, & Solodkin, 2002), further supporting the significance of our findings.

Our most disabled patient (P2) is the one who recruited more regions, which is in line with other studies mentioning greater injury to corticospinal systems correlated with greater recruitment of secondary motor areas(Pundik, et al., 2015; Ward, 2011). This patient also had a better recovery score after intervention, coinciding with some authors, who claim greater motor function gains obtained by severe patients at baseline(Pundik, et al., 2015). This increased activity can be interpreted as a compensatory mechanism that, when encountering a lesion, contributes to the maintenance of its functions by recruiting additional areas(Carey & Seitz, 2007). Thus, suggesting stroke-induced changes, in brain networks, are not exclusive to lesioned regions. The causes and consequences of such changes certainly merit consideration in future studies.

Our results are overall encouraging, although this study has several limitations, small sample size, which may have made us consider some changes as non-significant despite the fact that

they may be significant. This study would benefit from the inclusion of a follow-up phase post-intervention that would strengthen it. However, we designed it as a case series, the conclusions of which should be further explored and detailed in subsequent trials. Additionally, some of our regions of interest were severely damaged by the infarct, directly affecting BOLD signals, and likely justifying the difficulty in observing changes in other areas with enough statistical power.

Despite these limitations, we are confident that our main findings are robust enough to be considered, highlighting the potential for rehabilitation and neuroplasticity in chronic stroke patients.

Physiotherapy based on the Bobath concept approach throughout four weeks increased both the contralateral/ipsilesional precentral area activity and upper limb function in the chronic stroke patients from this study. Nevertheless, further research is needed so that an effective form of post-stroke rehabilitation may be considered.

Declaration of Interest: The authors declare that they have no conflict of interest.

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Brain-computer Interface combined with Physiotherapy: the efficacy of neurofeedback to enhance upper limb function and neuroplasticity in chronic stroke patients – a preliminary study

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Brain-computer interface combined with physiotherapy: the efficacy of neurofeedback to enhance upper-limb function and neuroplasticity in chronic stroke patients – a preliminary study

Abstract

This study aims to assess whether associating motor imagery with EEG-based Brain-Computer Interface (BCI) neurofeedback and a physiotherapy program can further enhance the neuroplasticity and recovery of upper-limb function in chronic stroke patients. A double-blinded, preliminary study with a pre-post intervention design was performed. Seven patients were randomly assigned to two groups, Experimental and Sham. Both did daily physiotherapy, the former associated with EEG-based BCI neurofeedback and the latter with sham neurofeedback, three-times-a-week for four weeks. Neuroplasticity and functional recovery were assessed using EEG symmetry index, functional magnetic resonance imaging, and several upper-limb clinical assessments (action research arm test, motor assessment scale and Fugl-Meyer assessment scale), before and after intervention. Minimal clinically important differences (MCID) were assessed. Patients and assessors were blinded to group assignment. Both groups improved in all functional outcomes, however gains in the Experimental group were above the MCID, after intervention, in three out of four outcome measures compared with two out of four in the Sham group. Moreover, subjects from the Experimental group displayed increased activation of the contralateral postcentral area and ipsilateral cerebellum and decreased functional asymmetry compared to the Sham group, during affected hand movement. This preliminary study expresses that motor imagery training guided through BCI-based neurofeedback can help improve upper-limb function and neuroplasticity in comparison to sham neurofeedback, in chronic stroke patients.

Keywords: Brain-machine interface, Neuroplasticity, Physical therapy, Rehabilitation, Stroke, Upper-limb recovery

Introduction

One-third of all stroke patients have poor or no residual hand motor function one year after stroke (Buch, et al., 2008), making this sequel one of the most common causes of chronic disability after stroke. Therefore, recovering upper-limb function in stroke patients is one of the major goals of neurorehabilitation (Page, et al., 2009). Motor rehabilitation has traditionally focused on conventional therapy, however recent methods, including motor imagery (MI) and brain-computer interface (BCI), have been gaining popularity as complementary treatments in recent years (Kaiser, et al., 2011).

MI-based mental practice training is defined as the internal rehearsal/simulation of an action without any evident physical movement (Sharma, et al., 2008; Page, et al., 2009). The benefits of MI seem to be dependent on physical practice (letskaart, et al., 2011). Nonetheless, there is evidence that MI can, by itself, promote cortical plasticity (Butler and Page, 2006), which is considered to be responsible for stroke rehabilitation (Cameirao, et al., 2010). One of the most essential motor-related networks, which contributes to this plasticity-guided recovery, is the one occurring between the contralateral primary motor cortex (M1) and the ipsilateral cerebellar hemisphere (Butler and Page, 2006; Sharma, et al., 2008). One main concern about MI is to ensure that it is adequately performed. Indeed, the “mental” nature of the task also makes it challenging both for therapists, who have no access to patients’ mind, and for patients themselves, who receive no feedback regarding their performance (Kaiser, et al., 2011). To address such difficulties, MI has been combined with BCI — a device capable of analyzing the brain activity and transforming it into visual, auditory or proprioceptive information for the patient, in a process known as neurofeedback (Daly and Wolpaw, 2008). Most of the research on stroke patients uses robotic devices and/or orthosis as a neurofeedback output, which is an expensive and not easily accessible resource (Buch, et al., 2008; Prasad, et al., 2010; Ramos-Murguialday, et al., 2013; AngChua, et al., 2015) when compared with visual or auditory outputs (Prasad, et al., 2010). The use of BCI systems has the potential for improving neuroplasticity by affecting motor learning, i.e., demanding closer attention to a motor task or requiring a specific brain signal activation/deactivation (Wang, et al., 2010). Additionally, it can promote functional enhancement due to its capacity to provide real-time neural activity feedback, which improves user performance (Wang, et al., 2010).

Surprisingly, while many authors have explored the impact of MI (with or without concomitant conventional therapy) in stroke rehabilitation, no study, to our knowledge, has analyzed the impact of associating BCI-based visual neurofeedback (real in comparison to sham) with MI and physiotherapy in order to increase the efficiency of the training in stroke. To overcome this lack of information, and provide the first data regarding this promising strategy, we developed the present study as a pilot trial for designing larger clinical trials in the future.

Our aim was to assess if BCI-based neurofeedback associated with MI training, as compared with MI alone (sham neurofeedback), improves the functional recovery of neuroplasticity and upper-limb function in chronic stroke patients.

Methods

Sample

Patients were recruited from the cerebrovascular outpatient clinic of a University Hospital after its ethics committee approved the study protocol. Patients with a first-ever episode of cortical infarct in the left middle cerebral artery (MCA) (≥ 12 months, which is considered sufficient time to stabilize) were prospectively selected. The selected patients were blindly and randomly assigned into two groups: daily physical therapy with simultaneous three-times-a-week EEG-based BCI real neurofeedback (Experimental) or sham neurofeedback (Sham), for four weeks. The infarct site was identified using structural MR or CT scans and was classified based on clinical and imaging criteria. Exclusion criteria were: hand plegia, persistent language and cognitive deficit (assessed by Montreal Cognitive Assessment (Freitas, et al., 2011) and Mini Mental State Examination), inattention, visual impairment, depression, inability to toilet themselves independently prior to their stroke, left-handedness (as assessed by the Edinburgh Handedness Inventory), inability to perform accurate motor imagery (i.e., score less than 75% in the hand-rotation component (Sharma and Baron, 2013)) and contraindications to magnetic resonance imaging (MRI). All subjects gave written consent according to the Declaration of Helsinki. None of the enrolled subjects dropped out of the study, and no unpleasant experiences with any assessment or therapy were reported.

Procedures

Neuroplasticity was assessed with EEG-fMRI as a primary outcome measure. Upperlimb function was assessed by using Action research arm test (ARAT), the Fugl-Meyer assessment scale – arm section (FMA), the Motor assessment scale (MAS) (Carr, et al., 1985; Van Der Lee, et al., 1999; Croarkin, et al., 2004; Yozbatiran, et al., 2008) and handgrip strength. The modified Rankin Scale (mRS) was used for measuring the degree of disability. Assessments were documented on video and, at the end of the experiment, two assessors blinded for intervention and moment, scored the patients based on video information as behavioral outcome measures.

Assessments were conducted in two different moments: one week before intervention (pre-treatment assessment (m1)) and one week after the four-week intervention period (post-treatment assessment (m2 - experimental condition)).

Motor and imagery paradigm to fMRI

The EEG-fMRI paradigm was a block design finger–thumb opposition sequence (30 seconds each) alternating MI or motor execution (ME) with a resting period for each hand, which was repeated five times. The order of the hands was random. ME was performed after MI since

activation patterns during MI can be influenced if preceded immediately by execution(SharmaBaron, et al., 2009). Finger movements during scanning were monitored by individual cameras.

EEG-fMRI data acquisition and processing

Setting: Siemens 3.0T (Siemens, Magnetom Vision, Erlangen, Germany), FoV: 245m, spatial resolution: 3x3x3mm³, TR 3s, TE 30ms, Flip Angle: 90°, 46 slices. FMRI analysis was processed in the Statistical Parametric Mapping software (SPM8 -<http://www.fil.ion.ucl.ac.uk/spm/>), using a standard pre-processing pipeline (slice timing correction, realignment, coregistration of structural and functional images, normalization and smoothing). Moreover, T1-weighted anatomical images of the entire brain were obtained with the following parameters: FoV 256 m; spatial resolution: 1x1x1.2mm³; TR = 2300ms; TE = 2.98 ms; flip angle 9°; 160 slices.

The EEG data was continuously collected at 10 kHz, using a 64-channel MRI-compatible system (MagLink by Neuroscan, Division of Compumedics Ltd., El Paso, TX) with electrooculogram and electrocardiogram electrodes. Electrode impedances were all kept below 5 kOhms. Gradient artifact and cardiac ballistic artifact were removed from the raw EEG data by template subtraction(Allen, et al., 2000) (Vision Analyzer, Brain Products, Germany). Data was down-sampled to 250Hz and low-pass filtered to 30Hz. The power spectral density (PSD) was estimated using Welch's method with 1-s windows and power estimates were averaged into the following bands: 8–13Hz (μ) (Sheorajpanday, et al., 2011) and 14-30Hz (beta) (Graziadio, et al., 2012). Two EEG channel pools were created: Central_left (lesioned site) as the mean of C1, C3, FC1 and FC3 channel PSDs and Central_right (non-lesioned site) as the mean of C2, C4, FC2 and FC4 PSDs. The EEG data during the 30-second rest condition was processed likewise.

The brain symmetry index (BSI) can have a significant predictive value for recovery in stroke being expected to be symmetric at rest in well-recovered patients(Sheorajpanday, et al., 2011; Graziadio, et al., 2012). According to the equation below, a value of 0 indicates absolute symmetric activity while a value of 1 indicates unilateral activity or asymmetry. The degree of symmetry in oscillatory activity was quantified during rest periods(Van Putten and Tavy, 2004) since no symmetry is expected during motor tasks.

$$\text{e. g. BSI during rest (BSI}_{\text{REST}}) = \left| \frac{C_{\text{left}} - C_{\text{right}}}{C_{\text{left}} + C_{\text{right}}} \right|$$

Consequently, the differences regarding the PSD between the lesioned and non-lesioned corticospinal system at cortical level were divided by their sum and expressed as an absolute value.

Behavioral assessment

The level of motor impairment was measured using the ARAT, the FMA(Van Der Lee, et al., 1999) and the MAS(Carr, et al., 1985). Each one of these clinical scores demonstrates good to excellent intrarater variability, reliability and all are valid in a stroke population(Croarkin, et al., 2004; Page, et al., 2009)The grip force was measured with Baseline® Hydraulic Hand Dynamometer three times, and the average value, scaled in kilograms, was used in the analysis. Patients were seated with their elbow flexed at 90 degrees and were not allowed to bring the instrument or arm into contact with their body, therefore having to exert the strongest grip possible(Prasad, et al., 2010).

Intervention

2.2.4.1. Physical Therapy based on problem-solving treatment

Physical therapy treatment involved 20 sessions(Paci, 2003; Luke, et al., 2004; Kollen, et al., 2009) of 50 minutes, five days a week(Luke, et al., 2004) during four weeks(Paci, 2003). The therapist who performed all treatments had more than ten years of experience in this therapy. The intervention content was organized in 5 major items: facilitated movement; mobilization; practicing an activity component and/or whole task and teaching patients (see Tyson, et al., 2009). Treatment strategies proposed aimed at both optimizing postural and movement strategies in order to enhance efficiency and maximize function and reducing the severity of impairments where they influence function (Huseyinsinoglu, et al., 2012). Therefore, all interventions, individually programmed, aimed at improving postural control of trunk and shoulder girdle in order to enable a more selective arm movement and increase strength and function (Vaughan-Graham, et al., 2014) to recover full motor range patterns (Levin & Panturin, 2011). Tasks were previously known and simple, with a functional goal not resembling the outcome measures. All interventions were administered at the patient's home. No other conventional therapy was applied.

2.2.4.2. MI training and BCI

The MI with an EEG-based BCI system involved 12 sessions of approximately 28-30 minutes, three times a week(Cameirao, et al., 2010), followed by the physiotherapy sessions; we established this order because otherwise, ME could influence MI. The MI task did not resemble those used in the outcome measures, particularly, during fMRI.

The EPOC (Emotiv®), a high-resolution multi-channel portable wireless neuroheadset composed of 14 active electrodes, was applied as the EEG acquisition device during MI. EPOC was connected wirelessly to a PC and subjects sat on an armchair while looking at a computer monitor placed at a 1-meter distance at eye level (figure 1).

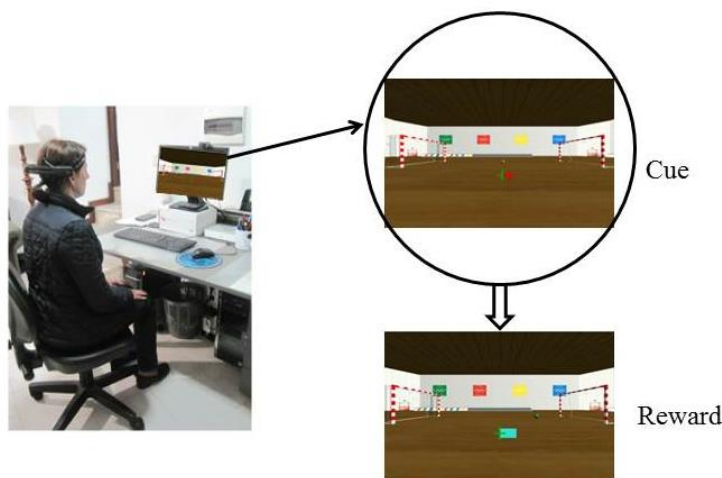


Figure 1: Example of a correct MI EEG-based BCI training in a handball arena, with a presentation of a fixation cross and a ball, followed by an arrow that overlaps the cross, pointing to the right (cue), and the respective reward (lightning bar and ball movement in the direction of the net).

Prior to intervention, the MI protocol was tested by the therapist on several age-, gender- and education-matched volunteers and standardized in terms of tasks and verbal commands. The final version of the protocol included the exact tasks and an exact word of instructions that was used with all subjects. The data from these, was collected.

During MI, patients were asked to keep their upper-limbs relaxed and to avoid eye movement during the recordings, since it is a key source of noise in EEG (Maskeliunas, et al., 2016). Each trial started with the presentation of a fixation cross and a ball at the center of the monitor in a handball arena (Figure 1), followed by an arrow overlapping the cross and pointing either to the right or the left (“cue”). Depending on the direction of the arrow, patients were instructed to imagine their right or left hand moving towards and touching the net. The sequence of right and left trials and the duration of rests between consecutive trials were random, as well as the timing between the display of the cross and the arrow. The experiment comprised four experimental runs of 40 trials each (20 left and 20 right). The “reward” was the visual movement of the ball on the screen in the direction of the goal (online, i.e., without delay). To help the patients understand the experience and use first perspective (i.e. imagine oneself execute the movement), together with MI during the first trial, the therapist assisted the movement of the affected limb in both groups, with a mean accuracy of 80% in Experimental and 78% in Sham. Moreover, during the pilot testing (and even during the intervention) some subjects had the ability to achieve an accuracy above 97.5%, suggesting that the patient, and not the BCI system, was responsible for the results. Thus, it seems that the variation depends on the subject and the accuracy is above the minimum required to control a BCI (Ahn and Jun, 2015).

In each trial, the verbal commands were standardized, for both groups, focused not only on the movement goal but also on the sensations associated to the movement itself, for example the sensation of elbow extension or feeling the net in the palm of the hand when the goal is achieved. As mentioned during the first trial, which served as calibration, the therapist assisted the movement of the affected limb in both groups, ensuring that all patients had the same information about which movement they should imagine. The main difference in the three subsequent trials was that Experimental had online feedback while Sham had visual feedback from data that was had been previously collected during the MI protocol training. The accuracy was pre-set above chance level, i.e., around 65%, in order to keep it positive, since negative or inaccurate feedback can hinder subjects and interfere with the performance/rehabilitation(Barbero and Grosse-Wentrup, 2010). Patients were blinded to the group allocation.

Data Analysis

Given the small number of subjects, non-parametric testing was used as implemented in SPSS 22 (IBM® SPSS® Statistics 22) for the statistical analysis. The Wilcoxon sign-rank test was used for the within-subject comparisons to relate behavioral scores, brain activation and BSI in m1 with m2 and brain activation in MI with ME, while the between-subject comparisons, (i.e. comparing the Sham and Experimental groups) used the Mann-Whitney test. Statistical significance was considered at $p < .05$.

In order to account for the functional heterogeneity of patients at baseline, a recovery score for behavioral outcome was calculated, i.e the sum of the differences between m1 and m2 for each score, divided by the total score at m1(i.e. the sum of all measures). Behavioral data was also analyzed based on the minimal clinically important difference (MCID), which represents the smallest amount of change in an outcome, as it might be important for the patient or therapist, due to the number of patients. The MCID was set at 10% of the total range of the scales, except for chronic patients who scored between 4.25 to 7.25 in FMA and 2.9Kg in grip strength(Van Der Lee, et al., 1999; Page, et al., 2012; Thielman and Bonsall, 2012). Statistical analysis of the fMRI data was performed using SPM8. For the first-level analysis, five conditions were modeled, namely rest periods, movement execution for the right (MER) and left hand (MEL) and movement imagination for the right (MIR) and left hand (MIL), with 30-seconds duration. For this study purposes, only contrasts representing motor execution and imagination of the affected hand were considered (i.e. MIR, MER), by contrasting the corresponding conditions with the baseline condition. Regarding the second-level analysis, due to the small sample size, and in order to reduce the number of multiple comparisons, a region of interest (ROI) analysis was set by averaging the contrasts of interest over each ROI. The ROIs considered were based on the right-hand sensorimotor execution network, i.e., precentral and postcentral, and cerebellum 6 and 8, whose influence on the M1 is well established. These regions were defined based on the Automated Anatomical Labeling (AAL) atlas(Tzourio-Mazoyer, et al., 2002).

Results

Study sample

Figure 2 demonstrates how the study population was recruited and managed during the study. Recruitment ceased at seven subjects due to the difficulty in finding eligible participants, given the strict inclusion and exclusion criteria.

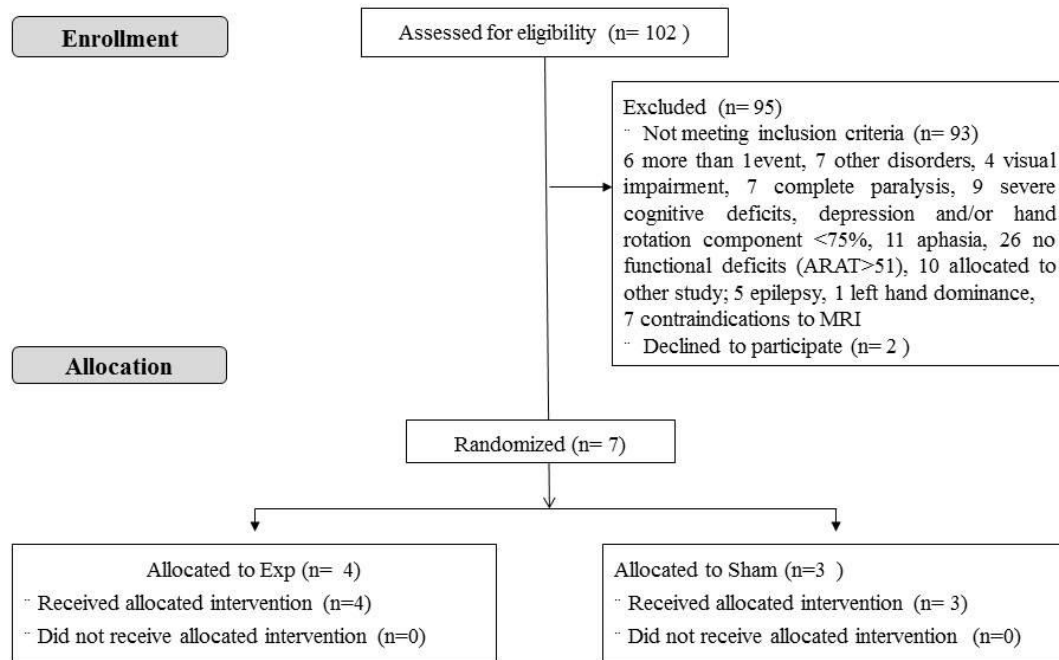


Figure 2: Flow chart diagram of the study (CONSORT 2010). Action research arm test (ARAT); Magnetic resonance imaging (MRI).

The groups were homogeneous regarding lesion location and gender. However, the Sham group had more time post-stroke and included a young patient, who had a moderate severity level (Table 1).

Table 1: Patient characteristics according to age, gender, lesion location, time post stroke, upper-limb function baseline (ARAT, MAS, FMA, grip strength), degree of disability and percentage of recovery score

Group	Age (years)	Gender (M/F)	Lesion Site	Time from stroke (months)	ARAT Baseline (/57)	MAS Baseline (/18)	FMA Baseline (/66)	Strength Baseline (Kg)	mRS x/6	Recovery Score (%)
Experimental	61	M	L MCA	66	49	18	57	20.05	2	18
	63	M	L MCA	13	37	12	31	7.78	3	21
	74	F	L MCA	40	16	6	22	5.83	4	20
	52	F	L MCA	14	41	17	46	16.63	3	14
Sham	66	M	L MCA	70	39	16	30	11.15	3	27
	36	F	L MCA	76	38	14	44	7.05	3	49
	61	F	L MCA	40	36	14	52	7.50	2	9

Abbreviations: Action research arm test (ARAT), Female (F), Fugl-Meyer assessment scale – arm section (FMA), Left Middle cerebral artery (L MCA), Male (M), Motor assessment scale (MAS), Modified Rankin Scale (mRS)

Clinical and Functional Recovery

No statistical differences were found between groups in different functional outcome measures, before and after the intervention. Table 2 describes the MCID reference values of each functional assessment and the values after 4 weeks (difference between m2 and m1 or gains). Patients from the Experimental group showed improvement in three of four outcome measures and all subjects had gains above MCID, with a recovery score between 14% and 21% (Table 1), whereas subjects from the Sham group only improved above MCID in the ARAT and FMA (between 9% and 42%). Surprisingly, overall gains were higher in the Sham group than in the Experimental one.

Table 2: Minimal Clinically Important Difference (MCID) reference values of ARAT, MAS, FMA and Grip Strength and gains after 4 weeks of intervention

Functional outcomes and MCID reference value	Experimental Median (p25;p75)	Sham Median (p25;p75)
ARAT_gains		
5.7 ($\pm 2sd$) points out of 57 total	5* (4.5; 6.3)	13* (10.3; 13.3)
MAS_gains		
1.8 points out of 18 total	0.3 (0; 0.5)	0.5 (-0.25; 2)
FMA_gains		
4.25 to 7.25 points out of 66 total (Chronic)	5.5* (3.8; 9.3)	11* (6.8; 14.8)
Strength_gains		
2.9Kg (chronic)	3.6* (0.2; 10.6)	1.2 (1.2; 8.4)
19.5% (orthopedic patients)	44.2%*	15.9%

* Higher than MCID

Abbreviations: Action research arm test (ARAT), Fugl-Meyer assessment scale – arm section (FMA), Minimal clinical important differences (MCID), Motor assessment scale (MAS), 25th-75th percentile (p25-p75)

FMRI findings

An increased activation was observed in ipsilateral cerebellum_6, contralateral precentral and postcentral during ME, as compared to MI of the affected hand (right).

No differences were found when comparing runs, i.e. baseline assessment (m1) with post-intervention assessment (m2).

Moreover, the groups showed similar results at m1 during MIR and MER, i.e. no differences were found between groups at baseline during right hand imagination and execution. Nonetheless, increased activity in ipsilesional postcentral and contralesional cerebellum 6 and 8 was observed in the Experimental group as compared to the Sham group (Figure 3), during MIR in m2, i.e., after intervention, but not during MER.

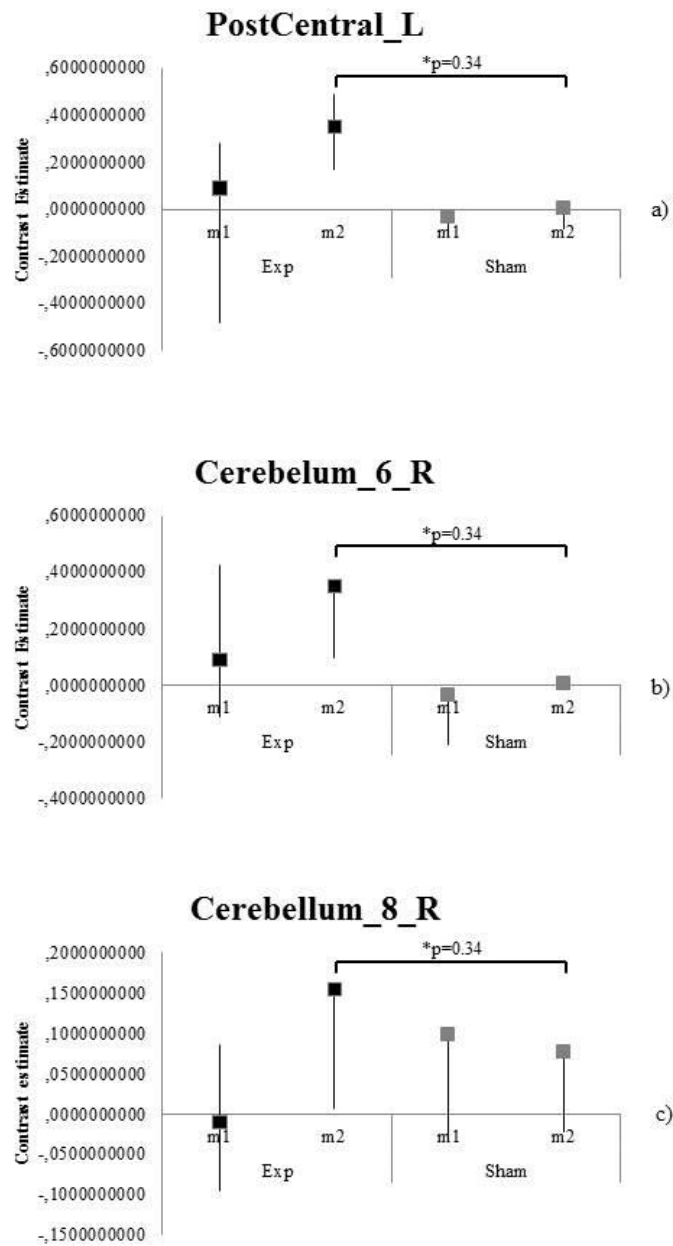


Figure 3: Median (and range) in activation values from postcentral left (a), cerebellum_6 (b) and 8 (c) right during MIR according to group (Experimental (black); Sham (gray)) before (m1) and after (m2) intervention. *p<0.05 between groups at m2

EEG findings

No statistical differences were found between groups or runs in BSI. However, independently of the frequency band (mu or beta), there was a tendency in the Experimental group to become more symmetric from m1 to m2 during the rest period. The Sham group demonstrated a more variable behavior, with an increased mu symmetry and beta asymmetry, as presented in Figure 4.

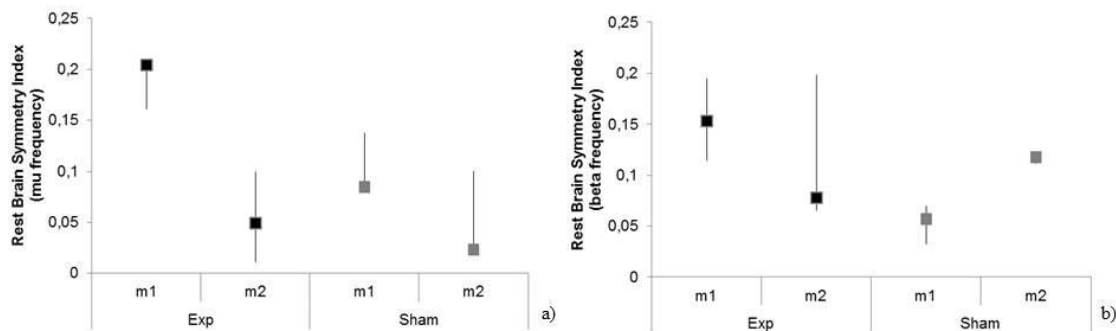


Figure 4: Brain symmetry index median (and range) by group (Experimental (black); Sham (gray)) at rest, at mu (a) and beta (b) frequency, before (m1) and after (m2) intervention.

Discussion

This study showed that using neurofeedback from BCI to guide MI might result in improved upper-limb function and neuroplasticity in chronic stroke patients, as compared to MI with sham neurofeedback. Nonetheless, the impact was modest and showed few changes regarding fMRI and EEG. As expected, both groups improved function, even in a chronic phase, but the Experimental group improved in more outcome measures (3 out of 4) and all subjects had gains above the MCID (Van Der Lee, et al., 1999). Interestingly, the results of the Sham group seem to be driven by one patient (the one with the most severe impairment at baseline), who had the most striking improvement. These findings might suggest that patients with better function have less ability to improve compared to patients with worse function, which has been a common finding in similar studies (Pundik, et al., 2015). This fact can be justified by the lack of specificity of the behavior outcomes or by the ceiling effect. As mentioned in a previous systematic review, the measurements recommended for assessing the efficacy of physiotherapy should target movement quality (Vaughan-Graham, et al., 2014). When patients achieve a higher functional state, it is important to assess not only the ability to perform it but also the correctness of the task.

Recent studies using a BCI system demonstrated an enhancement in the function of stroke patients. Similarly to what happened in the Experimental group, although with different outcomes, several studies(Prasad, et al., 2010; Caria, et al., 2011; Li, et al., 2014) mention along with clinical improvement, a normalization of brain activation patterns after intervention. Notwithstanding, some studies suggest the BCI system additionally benefits conventional or occupational therapy(Li, et al., 2014; Kim, et al., 2015), while others demonstrated that both control and experimental groups improved upper-limb function after intervention(Ang, et al., 2010; Ang, et al., 2014; AngChua, et al., 2015). In other words, in some studies, the use of BCI with robotic feedback showed less functional results than a repetitive training program, which suggests that the number of repetitions can be vital to recovery(Ang, et al., 2010; AngChua, et al., 2015). However, BCI groups have more long-term changes/results (not only does upper-limb function become better but it also keeps improving), suggesting that the observed recovery could be the result of a more “normal” brain activation, in terms of lateralization, induced by the central nervous system guided through BCI(Ang, et al., 2014; AngChua, et al., 2015). Thus, BCI training appears to strengthen neuroplasticity and may lead to better recovery(Varkuti, et al., 2013).

Considering the above, the analogous results concerning clinical improvement in our groups could be related to the similar amount of training, which provides identical functional results in the short term. On the other hand, a study which had an equal amount of BCI training and robotic feedback showed a significant recovery in hand function, with greater muscle activity in the intervention group as compared to the sham group(Ramos-Murguialday, et al., 2013); however, their gains were less than MCID.

The intensity of training may have influenced the better results in both the Experimental and the Sham groups. Two other studies with similar feedback and patient characteristics showed quite different results(Timmermans, et al., 2013). One showed no functional gains, despite the ability to manage orthosis with BCI(Buch, et al., 2008), while the other revealed an enhancement in both finger function and muscle activity of the affected extensors, even in patients with little or no motor function(Shindo, et al., 2011). These differences suggest that longer intervention with more time between sessions (Shindo, et al., 2011) might be more efficient than a more intense training (Buch, et al., 2008), since it may avoid fatigue. Patients, particularly women, often suffer from fatigue, making rehabilitation more demanding and worsening prognosis in both acute and chronic phases(Kutlubayev, et al., 2013; Miller, et al., 2013). In our study, all females had worse functional gains, except for one in Sham, possibly due to the fact of being the youngest subject. Therefore, the relationship between fatigue, gender and BCI performance should be addressed in a future study.

Not surprisingly, similarly to other studies with healthy volunteers or patients, our study revealed an enhanced activity in several brain areas during motor execution in comparison with the imagination of the affected hand(Sharma, et al., 2008; SharmaSimmons, et al., 2009). Notably, the Experimental group showed increased activity in the contralateral postcentral and ipsilateral cerebellum, as compared to the Sham group, after intervention during the imagination of the

right/affected hand. The cerebellum activity usually decreases shortly after stroke, maintaining those levels in chronic patients(Calautti, et al., 2007). The coupling between M1 and cerebellum is extremely affected in stroke patients(Mintzopoulos, et al., 2009); yet, greater cortical activity after stroke supports recovery(Favre, et al., 2014), thus suggesting less neuroplasticity recovery in the Sham group. Our data suggests better results in the Experimental group, although only during imagination, because the somatosensory cortex (located in the postcentral area) adds to the corticospinal track(Calautti, et al., 2007), while the cerebellum activity seems to compensate to assisting M1(Mintzopoulos, et al., 2009), crucial for an accurate reaching performance(Caligiore, et al., 2017). A “new” closed-loop circuit between the cerebellum and the postcentral area could be responsible for the activation observed, as the cerebellum influences not only M1 but also other cerebral areas(Caligiore, et al., 2017). It has recently been referred that the coupling of the cerebellum with the corticoreticular tract compensates the corticospinal track damage(Favre, et al., 2014) common in patients with middle cerebral artery stroke. Similarly, increased activity in the anterior cerebellar hemisphere was observed in healthy subjects, after non-dominant hand ability training, suggesting that the cerebellum anticipates a sensory outcome of action such as writing and increases performance(Walz, et al., 2015). Nonetheless, the opposite occurred in the lateral cerebellar hemisphere during sequential finger movements, which might demonstrate an economization process(Walz, et al., 2015). Further studies with stroke patients addressing the dominant hemisphere are required. The lack of results concerning the ipsilesional precentral area, during execution or imagination, could be related to the lesion itself, consequently preventing complete recovery. Furthermore, there is a correlation between the M1 and primary somatosensory cortex, and the laterality index in fMRI studies is well established, suggesting that the higher the activity in the direction of the ipsilesional hemisphere is, the lesser the motor deficit is.

A connection between precentral and postcentral areas in healthy subjects was also previously described, and these areas along with cerebellum after motor learning, particularly during an increase in accuracy(Mehrkanoon, et al., 2016), suggests an important role of the cerebellum in motor training in both mu and beta bands. Hence, the higher asymmetry observed at beta frequency in BSI at rest in the Sham group may imply less recovery, since beta is responsible for the disinhibition of the contralateral sensorimotor cortex and is associated with muscle execution over the motor cortex(Brinkman, et al., 2014). Thus, the asymmetry at rest may have influenced the task performance. New studies could be performed to analyze these types of correlations, since fMRI and EEG complement each other regarding spatial and temporal resolution, respectively.

Contrary to this study, an increased cortical activity (motor and premotor cortex) in the ipsilesional side during the motor execution task was described in another study, after intervention(Ramos-Murguialday, et al., 2013), probably due to the proportion of subcortical strokes in that study. This finding may be explained due to the fact that cortical strokes usually result in more serious chronic deficits and interfere with the laterality index, being more contralesional(Calautti, et al., 2007). Interestingly, although differences in the MI ability between cortical and subcortical strokes were reported in the literature(Luft, et al., 2004), and could have

also interfered with the ability to control a BCI system, however these differences did not hinder our findings.

The lack of greater differences/results in both groups after intervention in comparison with other studies using BCI(Ang, et al., 2010; Ramos-Murguialday, et al., 2013; Ang, et al., 2014; AngChua, et al., 2015; AngGuan, et al., 2015) may have resulted from the feedback provided, i.e., the lack of proprioceptive and kinesthetic information, which is important to guide movement but seems to be more controversial in severe patients(Buch, et al., 2008; Shindo, et al., 2011; AngChua, et al., 2015). The fact that feedback was kept above chance level, in Sham group, may have improved its performance, similar to what occurred in healthy volunteers(Barbero and Grosse-Wentrup, 2010). Ahn and Jun (2015) mentioned that the method of feedback can affect the psychological and physiological state of the user, and these are related with BCI performance, thus creating a cycle. The same authors proposed several strategic approaches to overcome performance variation, for example practicing kinesthetic and goal-directed MI, which is similar to the one we used(see Ahn and Jun, 2015). The low performance variability between subjects and high accuracy levels that occurred in our study in contrast to others could be not only due to the calibration being performed with both MI and movement execution but also since we had assessed the MI ability prior to the intervention in all subjects, which reduced the BCI illiteracy(Maskeliunas, et al., 2016). It has been recently mentioned that, although EPOC can interfere with user BCI-illicit, this device may be more suitable for controlling tasks using attention compared to other low-cost consumer-grade EEG devices (Maskeliunas, et al., 2016). A more intuitive interface with better hardware or software (including algorithms) was stated to contribute to improvements in users performance (Ahn and Jun, 2015). Furthermore, both groups performed MI combined with physiotherapy and, as stated, MI coupled with repetitive physical practice can improve function(Page, et al., 2009; Arya, et al., 2011) and induce larger cortical changes, leading to cortical reorganization and functional outcome improvement(Butler and Page, 2006). Contrary to this study, despite brain activity changes, it seems that function enhancement occurs only with somatosensory feedback, as compared to visual feedback(Ono, et al., 2014), thus reinforcing the idea that physiotherapy needs to be associated with BCI training when robotic feedback is not possible. Nonetheless, our results suggest that BCI combined with therapy is an auxiliary rehabilitation tool for upper-limb rehabilitation after chronic stroke, since a cognitive demand helps patients to focus on the affected hand. Therefore, BCI training modulates brain activity at rest and throughout the different tasks, explaining the increased symmetry in the Experimental group at rest after intervention.

One of the most important limitations of the present study is the small sample size. However, it is worth noting that this is a preliminary study using a novel, putatively more robust methodology. Indeed, to our knowledge, it is the first study designed using a real sham neurofeedback intervention, without orthosis or transcranial direct current stimulation, providing a very preliminary estimate of the results of such intervention. This will allow future studies to predict the impact of including such an arm in their design and more accurate prediction concerning the effect size and sample sizes needed. In addition, it can also support, in the near future, the adoption of a higher minimum accuracy level (our results showed that all patients can have

accuracies above 75%), in neurofeedback trials. The sample heterogeneity may also have limited our results, nonetheless it also has some strengths. MI ability(Sharma and Baron, 2013) was assessed in all subjects, each group had a similar number of male and female participants (Schaechter and Perdue, 2008; Schuster, et al., 2011) and a good stratification regarding age(Saimpont, et al., 2009), lesion location and handedness was taken into account(Carey and Seitz, 2007; Ward, et al., 2008). The recovery score was normalized to baseline values to annul baseline differences among subjects. Larger trials of BCI in stroke population are required to confirm our results and to clarify some literature controversial concerning this topic. Follow-up assessments are necessary to verify if the observed brain symmetry is converted into function in the Experimental group.

The findings suggest that MI training guided through neurofeedback contribute to the improvement of upper-limb function and brain symmetry in chronic stroke patients.

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Discussion

The emergence of new techniques and procedures such as MI and BCI in order to help conventional therapies such as constraint-induced modified therapy (CIMT) (Page, Dunning, Hermann, Leonard, & Levine, 2011) in neuroplasticity enhancement and consequently recovery of upper limb function is a current phenomenon. Nonetheless, the most commonly used is PT though its efficiency is still a matter of debate (Vaughan-Graham, Cott, & Wright, 2014). Yet, recently PT intervention has been stated to improve at least one functional measure and have similar efficacy as CIMT. This data was the trigger to this thesis. Being PT a more inclusive approach, i.e. being applied to any degree of functional severity contrary to CIMT, the absence of evidence (Vaughan-Graham, et al., 2014) and since MI is an adjunctive treatment to PT (Meadows, Raine, & Lynch-Ellerington, 2009), this study consists of three parts with distinct aims, which are compatible among each other, and as demonstrated, their results interact.

As reviewed in chapter 1.2, the increased evidence in MI in stroke intervention shows that stroke patients have the ability to perform it (Page, et al., 2011), especially with familiar tasks, even in severe cases with total absence of functional movement. However, results are not always transferred to daily life activities or result in functional recovery. It seems when MI is added to conventional therapy in chronic stroke patients (Page, et al., 2011) it results in better recovery than when embedded or in acute phases (Bovend'Eerd, Dawes, Sackley, Izadi, & Wade, 2010; Ietswaart et al., 2011). It is still controversial the adequate dosage time for these patients (Dickstein & Deutsch, 2007; Page, et al., 2011), being quite variable in many studies not only in terms of number of sessions (12 to 30) or days-week (2 to 3) but also in duration (30 to 60 minutes). Additionally, MI was also found to induce neuroplasticity since it involves motor planning areas (e.g. SMA) as well as M1 (Hanakawa, Dimyan, & Hallett, 2008; Sharma et al., 2009) suggesting that it can contribute to improve motor recovery in subcortical strokes (Butler & Page, 2006; Sharma, et al., 2009). Nevertheless, studies mentioned the difficulty in integrating MI in clinical practice (Bovend'Eerd, et al., 2010) therefore, the need for new tools to help therapists/patients control MI execution, just as a BCI, is essential. Recently, several studies with robotic BCI systems have been applied to stroke intervention (Ang et al., 2010; Buch et al., 2008; Shindo et al., 2011; Varkuti et al., 2013), which not only gives visual but also kinesthetic and proprioceptive feedback, however, with some contradictory results. Robotic arms are both an expensive and inaccessible resource (Prasad, Herman, Coyle, McDonough, & Crosbie, 2010) and

also lack movement variability with few degrees of freedom compared to normal movement. Seeing that stroke patients have limited options due to compensatory strategies, stereotypic movement and consequently, less variability (Meadows, et al., 2009), robots may not be an advantage. The use of an open source tool, easy to access, can be useful and save money to patients and caregivers.

Nonetheless, issues are raised: can PT change recovery and neuroplasticity in chronic patients?; Is a 4-week program enough to induce changes? Moreover, considering that MI ability is essential to BCI control, we question if the gains derive from neurofeedback, MI, or the combination of both. Given these findings, MI training was added to an EEG-based BCI after a PT session and it was analyzed in order to determine if neurofeedback or MI did in fact aid recovery.

In this sense, the first task of our study was to assess the neuroplastic and functional changes and compare the effect of a 4-week PT to no intervention. The healthy subjects served as a reference of changes in EEG-fMRI while the patients and respective period of no intervention, served as the control for the second task of this thesis.

The second task of the study compares the effect of real neurofeedback from BCI training to sham neurofeedback from BCI training in association with PT sessions. When we started to analyze data, we became aware of the need to understand better the correlation between BSI and BOLD changes modulated by multiple tasks for both hands in chronic stroke patients, along with its relationship with factors that can interfere with recovery, which is different from those used in previous studies.

Correlations between BSI and fMRI

Contrary to what was expected, age and particularly baseline function did not correlate with the activity of any ROI (Calautti et al., 2007; Ward, Brown, Thompson, & Frackowiak, 2003). Outstandingly, time since stroke influences the activity of right cerebellum, i.e. an increase in months post stroke related to a decrease in cerebellum activity (Chapter 2.1). The latter correlation can be justified by the loss of right hand use or in this case, by the lack of multiple feedback loops between M1 and the cerebellum (Dong, Winsten, Albistegui-DuBois, & Dobkin, 2007). This data suggests that cerebellum can be an important goal of rehabilitation (Mintzopoulos et al., 2009), referred to below.

We found that real BSI demonstrated an increased asymmetry during motor execution or imagination in stroke patients through the contralesional hemisphere, which is contrary to healthy

subjects and to patients with good recovery (van Putten & Tavy, 2004). However, although BSI could be asymmetric, we found that patients who are able to change their brain activity through the affected hemisphere, are able to increase activity from that side, information that could be lost with an exclusive BSI analysis without fMRI, suggests the importance of a combined analysis in the future.

Another interesting finding is that the dominant hand has different activities and strategies compared to the non-dominant hand, justifying our differences between affected and unaffected hand and the lack of correlations in the latter. Furthermore, alpha/beta rhythms are functionally coupled with the BOLD signals and bilateral increased activity was observed. One of the more important areas was SMA, which is in line with other studies that mention the importance of SMA in recovery and movement regulation, since it provides the link between the sensorimotor cortices (Serrien, Strens, Cassidy, Thompson, & Brown, 2004), however, the main correlations were only observed at beta band. Nonetheless, it seems that stroke patients have different strategies presenting less non-primary motor areas correlated to the unaffected compared to affected hand movement execution. Thus, it is important to explore and understand the SMA role in stroke rehabilitation.

Effect of physiotherapy based on the Bobath Concept in upper limb function and neuroplasticity

In Chapter 2.2, we confirmed previous observations that motor execution implies greater activation compared to MI and patients showed an overactivation at baseline during movement of the affected hand compared to healthy subjects. Moreover, both healthy and stroke patients recruit bilateral areas. Furthermore, the ability to perform MI was affected in patients with cortical stroke at baseline. Despite the low number of subjects, our results are in line with previous ones.

Besides, some studies stated that a decreased activity is correlated with patient improvement (Dong, et al., 2007; Rossini, Calautti, Pauri, & Baron, 2003), however, our results suggest that this can be due to learning, because the decreased activity observed in 2 out of 3 patients was not related with recovery (Ward, et al., 2003). Additionally, since previous studies do not have a third assessment, we do not have a base of comparison. More recently, similar to our study, different activation strategies according to severity were demonstrated, i.e. an increase or a decrease after intervention depends on patient severity (severe or mild, respectively) (Pundik et al., 2015). Contrarily, our results demonstrated that independently of being severe or mild, an increased

activation in bilateral cerebellum occurred during MER, suggesting that despite the individualized intervention common in PT, patient training was directed to the recommended somatosensory-guided learning based (Westlake, Hinkley et al. 2012). These results are encouraging because even in a chronic phase, PT was able to change cerebellum activity and as previously mentioned, it is influenced by time post stroke.

In summary, our experimental work showed for the first time, that a short-time intervention based on problem-solving induces functional recovery and is accompanied with neuroplastic changes in chronic stroke patients.

Physiotherapy based on the Bobath Concept versus Brain-Computer Interface: combined approach

To finalize, it seems that MI training guided through real neurofeedback from BCI can improve upper limb function in chronic stroke patients compared to sham neurofeedback (Chapter 2.3). We realized that function improved in both groups yet, the BSI was higher in the former and showed increased activity in the contralateral postcentral and ipsilateral cerebellum, after intervention during the imagination of the right/affected hand. Thus, since an increased activity in cerebellum is usually a compensation to assist M1 and is part of the “new” closed-loop circuit between the cerebellum and the postcentral area (Caligiore, et al., 2017), this data suggests a better strategy. Furthermore, the variability in the BSI in the sham group also suggests poorer performance compared to real neurofeedback.

Nonetheless, recent studies using a robotic feedback allied to a BCI system demonstrate a functional improvement as well as an increased cortical activity, a normalization of brain activation patterns and even higher muscle activity (Caria et al., 2011; Ramos-Murguialday et al., 2013; Varkuti, et al., 2013), which can be the result of the kinesthetic and proprioceptive feedback, i.e. the main difference with our study. Although this can justify the differences, particularly the neuroplastic changes, some aspects such as lesion location (subcortical) and phase (acute) may have interfered.

Currently, it has been stated that, independently of the functional improvement, severe patients increased their brain activation while mild patients with a better motor function at baseline decreased it (Pundik, et al., 2015), so, a variability in function at baseline can make the group analysis difficult justifying our lack of results in fMRI.

The following issue remains, did mental training lead to the recovery or was neurofeedback waived? On the other hand, did neurofeedback keep patients motivated and lead them to paying better attention through action independently of being real or sham? More studies must be performed.

Limitations

The current study presents some limitations. Despite the fact of trying to create rigorous inclusion and exclusion criterions (based on aspects that interfere with MI and to ensure safety), and the randomization based on some of these criterions (age, gender, severity), unfortunately these resulted in a small sample size with a heterogeneity of lesions which became our main limitation. Although the enrollment occurred in one of the major hospitals in Porto, during 3 years, from the 102 screened chronic patients, only 10 did not fail to meet the inclusion criteria. The main reasons were because of family doctor referrals and the inability to assess those patients.

Due to the limitations of intervention time (4-weeks) and the possibility of neglect seeing that dominant hemisphere lesions and neglect had less ability to produce MI, we excluded right MCA stroke so, our results only relate to left MCA stroke patients because 4-weeks might not be sufficient to induce either functional or neuroplasticity changes.

The use of an abstract feedback instead of a realistic feedback, or even adapted to patient preferences might have interfered with motivation in performing the MI, however we tried to prevent fatigue and discouragement alternating training days. We also used feedback around chance-level in the sham group to avoid bias of results.

The lack of a group that only had PT intervention was also a limitation because we do not know if results are due to MI based on BCI system or PT itself. Ethically, we performed PT intervention after a period of non-intervention seeing that learning affects the fMRI data, which consequently was not used. Nonetheless, our real neurofeedback induced more brain symmetry.

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Conclusion

This study aims to analyze the neuroplasticity and functional changes in chronic stroke patients after a PT intervention, alone and combined with a MI with neurofeedback EEG-based BCI.

Based on our results, we concluded that:

1. Months post stroke interfered with contralateral cerebellum activity, decreasing it. Bold changes were positively correlated with the EEG asymmetry, the higher the brain asymmetry through the affected hemisphere, the higher the activity from that hemisphere thus contradicting the brain asymmetry through the unaffected hemisphere that characterizes stroke patients in affected hand movement (Chapter 2.1).
2. A PT program of 4-weeks promoted not only recovery of upper limb function but also neuroplasticity changes (increasing ipsilesional precentral area activity during execution) even in chronic stroke patients (Chapter 2.2)
3. MI training guided through neurofeedback (real or sham) from BCI contributed to the improvement in the upper limb function and brain symmetry in chronic stroke patients, particularly the former (Chapter 2.3).

Future Perspectives

This thesis contributes to a better acknowledgement of PT efficacy not only in function but also in neuroplastic changes. Moreover, a better comprehension about MI guided through a BCI system and respectively neurofeedback as outlined in the beginning of this work. Still, many other issues were raised and new pathways should be explored in future research.

Independently of the study, the inclusion criterions should be even more rigorous, selecting patients, severe or mild, since it interferes with the BOLD signal and to allow group analysis.

It is important to look at BSI critically since it alone does not reflect the activation of the ipsilesional hemisphere. This study suggests that different hand dominance can interfere with brain activation and correlation between BOLD and BSI and can differ if the stroke was in the non-dominant hemisphere.

Relatively to the aims, PT being an individualized intervention, and frequently criticized for this, it is important to explore how the practice of the part and/or whole task is directed towards learning and how it relates with cerebellum neuroplastic changes.

Despite the small sample, the results were encouraging seeing that a simple mental training such as the reaching movement of touching the goal net with the hand, results in a more symmetric brain activity and helps the function of the affected limb. We considered that the study of ideal/accurate feedback, adapted to personal preferences should be performed, i.e. isolated and combined functional movement (hand and/or arm focused), such as tasks adjusted to daily activities according to patient needs and difficulties (reach, grasp, grip, coordination,...) then the corresponding visual feedback, seeing that robots are an expensive technology.

Annex I

**Brain-computer Interface in Upper Limb Recovery in Stroke Patients: A
Systematic Review**

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Manuscript under preparation

Abstract

BACKGROUND AND PURPOSE: Technologies such as brain-computer interfaces are able to guide mental practice, in particular motor imagery performance, to promote recovery in stroke patients. The aim of this review is to provide a status report regarding advances in brain-computer interface, focusing in particular in upper limb motor recovery.

METHODS: PubMed, Scopus and PEDro database were systematically searched for articles published between January 2010 to December 2017. The selected studies were randomized controlled trials involving brain-computer interface interventions in stroke patients, with upper limb assessment as primary outcome measure. Reviewers independently extracted data and assessed the methodological quality of the trials, using the PEDro methodologic rating scale.

RESULTS: From 309 titles, we included ten studies with high quality (PEDro $\geq$ 6).

DISCUSSION: We found that the most common interface used was electroencephalography and the main neurofeedback, in stroke rehabilitation, is usually visual abstract or a combination with the control of an orthosis/robotic limb. Moreover, the Fugl-Meyer assessment scale was major outcome measure in nine out of ten studies. In addition, the benefits of functional electric stimulation associated to an interface were found in two studies, though there was no coherence between them.

CONCLUSIONS: Neurofeedback training with brain-computer interface systems seem to promote clinical and neurophysiologic changes in stroke patients, in particular those with long-term efficacy.

Keywords: Arm; brain-computer interface; brain-machine interface; stroke; upper limb;

Introduction

Upper limb motor rehabilitation in stroke patients has traditionally relied on conventional therapies (e.g. physiotherapy, occupational therapy,...), however, newer methods, including motor imagery (MI)-based mental practice and brain-computer interface (BCI) are gaining popularity. MI involves a structured and purposeful repetition of movements using imagination, with no motor output or evident motion(Arya, Pandian, Verma, & Garg, 2011; Jeannerod, 1995; Saimpont, Pozzo, & Papaxanthis, 2009), and shares several cognitive aspects with motion/action(Jeannerod, 1995; Page, Levine, & Khoury, 2009). Numerous systematic reviews in MI demonstrate its efficacy in upper limb recovery(Barclay-Goddard, Stevenson, Poluha, & Thalman, 2011; Braun, Beurskens, Borm, Schack, & Wade, 2006; Garcia Carrasco & Aboitiz Cantalapiedra, 2013; Kho, Liu, & Chung, 2014; Nilsen, Gillen, & Gordon, 2010; Zimmermann-Schlatter, Schuster, Puhan, Siekierka, & Steurer, 2008). Nonetheless, one main concern is to ensure that mental activity is being adequately performed when applying MI to motor rehabilitation. Indeed, the “mental” nature of the task makes this verification difficult both for therapists who have no access to the patient’s mind, and patients who receive no feedback regarding performance(Kaiser, Kreilinger, Muller-Putz, & Neuper, 2011). To address such difficulties, there have been some attempts to combine MI with BCI. The latter may involve functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) or electroencephalography (EEG)(Ang & Guan, 2013; Nicolas-Alonso & Gomez-Gil, 2012) capable of analysing the activity in a patient’s brain and transforming it into visual, auditory and/or proprioceptive information, which is then sent back to the patient in a process known as neurofeedback(Silvoni et al., 2011). Thus, if MI contributes to re-establishing motor function by inducing activity-dependent brain plasticity(Ietswaart et al., 2011), the use of BCI can further

enhance neuroplasticity by affecting motor learning, i.e., promoting closer attention to a motor task or requiring the activation or deactivation of a specific brain signal(Daly & Wolpaw, 2008; Dobkin, 2007; Pichiorri et al., 2015). According to several studies(Ang & Guan, 2013; Nicolas-Alonso & Gomez-Gil, 2012; Soekadar, Birbaumer, Slutzky, & Cohen, 2015; Wang et al., 2010), BCI systems seem to have the potential to promote functional recovery after stroke given its capacity to provide real-time neurofeedback, which improves user performance, not only in BCI accuracy but also in upper limb function. Coincidentally, a review was recently published. It mentioned that BCI based on EEG intervention is a promising rehabilitation approach in stroke patients(Monge-Pereira et al., 2017). However, despite this, there is a need for constant updates of evidence and a more in-depth analysis as a result of the increasing numbers of publications and developments made in this specific area of expertise. Therefore, the main objective of this systematic review is to assess the scientific evidence concerning the effectiveness of BCI intervention in the rehabilitation of upper limb function in stroke patients followed by its systematization. Additionally, we aimed to provide recommendations for future research/study in this field based on the findings.

Methods

Figure 1 depicts an overview of the research strategy, selection criteria and quality assessment.

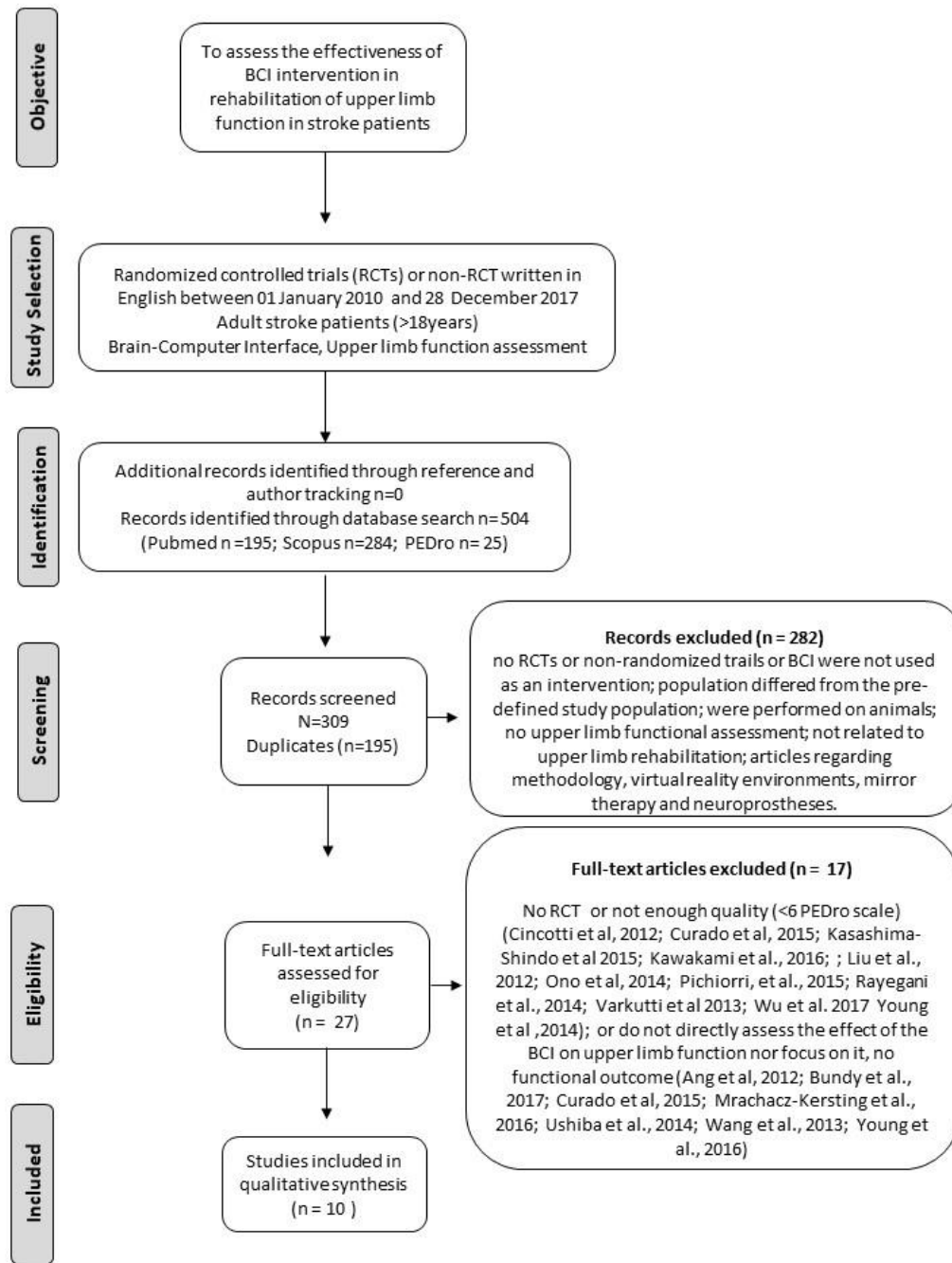


Figure 1: Overview of literature search. BCI- Brain Computer interface; RCT- Randomized Controlled Trial

Data Source and Searches

Researchers used the electronic database PubMed, Scopus and PEDro. Researched terms included in Pubmed and Scopus: (stroke or hemiparesis or hemiplegic), and (brain-computer interface or brain-machine interface or neurofeedback), and (upper limb or upper extremity or

arm or hand). The database was checked for pre-defined MeSH terms, which were integrated in the research strategy. The detailed research strategies are available upon request. For the PEDro database we performed three simple searches for the following keywords: brain-computer interface, brain-machine interface and neurofeedback.

Study Selection

The selected studies in the review were included only if they met the following criteria: published in English or Spanish between 01 January 2010 and 28 December 2017; focused on the effects of BCI training in improvement of upper limb function or reduction of upper-extremity impairment in adult stroke patients; had no restrictions concerning time since onset of stroke or lesion type (ischemic or haemorrhagic); and, at least one clinical outcome measure, addressing upper limb function, had to be used (e.g. Fugl-Meyer...). The levels of evidence considered for this review were Level I (randomized controlled trials, or RCTs) or Level II (nonrandomized trials). We excluded studies in non-human or healthy subjects, review papers, methodological or descriptive papers or even, studies, which only analysed cortical mechanisms of BCI using measurements such as fMRI or diffusion tensor imaging (DTI) in the absence of functional assessment. Studies with virtual reality environments, mirror therapy and neuroprostheses were also excluded.

Type of intervention

BCI training could have been added to conventional therapy, embedded in the therapy or included as an independent intervention. Studies in which BCI practice were non related to upper limb movement (hearing, odour, any kind of visual imagery with static pictures) nor focused on the direct effect of BCI on upper limb function, i.e. studies that did not study the intervention effect of a BCI training and, were merely descriptive, were excluded.

Type of outcome

Since upper limb function deficits remain after stroke, thus interfering with one's participation in society after returning home (Page, et al., 2009), studies were selected when at least one measure assessed upper limb function using observational (e.g. Fugl-Meyer Assessment (FMA)) or instrumental methods (e.g. grip strength).

Data extraction and Quality assessment

The initial screening of the article list was by title and abstract, and was reviewed manually, to avoid missing any crucial article by using specific electronic search tools, except for publication dates. Whenever information in the abstract was not clear, especially whether the study was to be included or not, the full article was considered. Reviewers recorded the details of each study using a predefined form concerning study design, population examined (age, gender and time since stroke), interventions such as intensity of treatment and type of neurofeedback, outcome measurement methods, and results/conclusions.

Independent screenings of the article abstracts and decision about which ones could potentially meet the inclusion criteria, were carried out by the authors. When lack of consensus occurred, the researchers held discussions to achieve an agreement.

The methodological quality of the studies was assessed by using the Physiotherapy Evidence Database (PEDro) Scale, which is based on the Delphi list (Moseley, Herbert, Sherrington, & Maher, 2002). This tool has 11 items, two additional items not on the Delphi list (PEDro scale items 8 and 10). The items are described in table 1. Methodological criteria were scored as: yes (1 point), no or do not know (0 points). The maximum possible score was 10, with a range of 0–10. Studies were considered to be of high quality when they met six or more items (good to excellent). The PEDro scale showed good reliability and interrater reliability (Olivo et al., 2008).

Data Synthesis and Analysis

We summarized the results of the data extraction and the quality assessment in structured tables.

Results

Study selection

From the above-mentioned databases, 504 articles were found, 195 were duplicated and from the remaining 309, 26 articles and one book chapter were included in this study, for closer evaluation. The main reasons for excluding the other 282 (by title and/or abstract) is described in figure 1. From the 27 articles remaining, 17 were excluded after reading the full-document(Ang et al., 2012; Bundy et al., 2017; Cincotti et al., 2012; Curado et al., 2015; Kasashima-Shindo et al., 2015; Kawakami et al., 2016; Mrachacz-Kersting et al., 2016; Ono et al., 2014; Pichiorri, et al., 2015; Rayegani et al., 2014; Varkuti et al., 2013; Young, Nigogosyan, Walton, et al., 2014; Young et al., 2016)(Liu et al., 2012; Ushiba, 2014; Wang, 2013; Wu et al., 2017)(see Figure 1). No new articles were retrieved by using reference and author tracking. After quality assessment, ten studies were considered since they had a score of 6 points or more, therefore considered to have sufficient methodological quality(Ang, Chua, et al., 2015; Ang et al., 2010; Ang, Guan, et al., 2015; Ang et al., 2014; Frolov et al., 2017; Jang, Kim, & Lee, 2016; Kim, Kim, & Lee, 2015; Li et al., 2014; Mihara et al., 2013; Ramos-Murguialday et al., 2013) (table 1).

Table 1: Quality assessment of internal validity of the RCTs with the PEDro Scale.

	Ang, et al., 2010	Ang, Chua, et al., 2015	Ang, et al., 2014	Ang, Guan, et al., 2015	Frolov, et al., 2017	Li, et al., 2014	Ramos-Murguialday, et al., 2013	Jang, et al., 2016	Kim, et al., 2015	Mihara, et al., 2013
1. Eligibility criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
2. Random allocation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Allocation was concealed	No	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes
4. Baseline comparability	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Blind subjects	No	No	No	Yes	No	No	Yes	No	No	Yes
6. Blind therapists	No	No	No	No	No	No	Yes	No	No	No
7. Blind assessors	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
8. Adequate follow-up	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
9. Intention-to-treat analysis	No	No	No	No	No	No	No	No	No	No
10. Between-group comparisons	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Point estimates and variability	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

For a summary of all study characteristics, such as population, intervention protocol and its duration, BCI sessions and neurofeedback, measures instruments and main results/conclusions with regard to the effects of BCI on physical recovery see Table 2.

Table 2: Overview of study characteristics of included RCTs: stroke population.

Study	Method/ Population (age, gender, time of onset)	Intervention protocol and duration		BCI sessions and neurofeedback	Measures Instruments, moments and follow-up	Results/Conclusion with regard to the effects of BCI on physical recovery
		Intervention for E /C(w/f/min)	Rehabilitation Period			
Ang, et al., 2010	<p>RCT</p> <p>N Total=25 N EG=11 N CG=14</p> <p>Mean age, SD (years) EG=47.5 ±13.5 CG= 53.1 ± 8.6</p> <p>time post stroke (mths) EG=12.6±9.56 CG=8.2±6.04</p> <p>Type (I/H) EG=5I/6H CG=5I/9H</p> <p>Side (R/L) EG=6R/5L CG=9R/5L</p> <p>Gender (M/F) EG=9M/2F CG=7M/7F</p>	<p>1-hour rehabilitation sessions:</p> <p>EG - EEG-based MI-BCI with robotic feedback (122 trials)</p> <p>CG - Robotic rehabilitation (960 trials)</p> <p>3d/wk.</p>	<p>4wks (12 sessions)</p>	<p>A visual cue on a screen (8-point clock face–drawing interactive video game) and then instructed subject to perform MI (affected) or motor execution (unaffected).</p> <p>Visual and Kinaesthetic and proprioceptive feedback: the MIT-Manus robot (Interactive Motion Technologies USA, Watertown, MA) moves the affected limb towards the goal.</p>	<p>FMA</p> <p>Timing: - Pre-test, 2wks and 4wks after the start of the intervention</p> <p>- Follow-up 2 mths after post-test</p>	<p>Both Groups improved after 4 wks. of treatment</p> <p>EG 4.5±6.1 CG 5.3±6.3</p> <p>and 2 mths post-rehabilitation EG 6.2±6.3 CG 7.3±9.4</p>

Ang, Chua, et al., 2015	<p>RCT N Total=25 N EG=11 N CG=14</p> <p>Mean age, SD (years) EG=48.5 ±13.5 CG= 53.6 ± 8.6</p> <p>time post stroke (mths) EG=12.6±9.55 CG=7.7±6.04</p> <p>Type (I/H) EG=5I/6H CG=5I/10H</p> <p>Side (R/L) EG=6R/5L CG=9R/6L</p> <p>Gender (M/F) EG=9M/2F CG=7M/7F</p>	<p>1,5-hour rehabilitation sessions:</p> <p>EG - EEG-based MI-BCI with robotic feedback (136 repetitions/session)</p> <p>CG - Robotic rehabilitation (1,040 repetitions/session)</p> <p>3d/wk.</p> <p>Without standard physical therapy</p>	4wks(12 sessions)	Identical to Ang et al. (Ang, et al., 2010)	<p>FMA</p> <p>Timing: - Pre-test, 2wks and 4wks after the start of the intervention</p> <p>- Follow-up 2 mths after post-test</p>	<p>Both Groups improved after 4 wks. of treatment</p> <p>EG 4.5 (+17,1%) CG 6.3 (+23.5%)</p> <p>and 2 mths post-rehabilitation a percentage of patients keep improving EG 63.6% CG 35.7%</p> <p>No differences between groups</p>
Ang, et al., 2014	<p>RCT</p> <p>N total =21 N EG1 =6 N EG2 =8 N CG =7</p> <p>Mean age, SD (years)</p>	<p>1-hour</p> <p>EG1 - EEG- based MI-BCI with Haptic Knob robot (120 trials)</p> <p>EG2 - Haptic Knob robot (120 trials)</p>	6wks(18 sessions)	Four different visual cues on a screen and then instructed subject to perform MI combined with kinaesthetic and proprioceptive feedback: Haptic Knob robot that assisted	<p>FMA</p> <p>Timing: - Pre-test, 3ws and 6wks after the start of the intervention</p> <p>- Follow-up 6 and 18wks after post-test</p>	<p>All groups improved after the 6 wks. treatment EG1 7.2 ± 2.3 EG2 7.3 ± 4.7 CG 4.9 ±4.1</p> <p>During follow-up only the experimental groups kept the improvement</p>

	<p>EG1 =54.0 ± 8.9 EG2 =51.1 ± 6.3 CG = 58.0 ± 19.3</p> <p>time post stroke (mths) EG1 =9.4 ± 2.10 EG2 =13.1 ± 4.96 CG =14.9 ± 3.60</p> <p>Type (I/H) EG1=2I/4H EG2=4I/4H CG=5I/2H</p> <p>Side (R/L) EG1=4R/2L EG2=3R/5L CG=3R/4L</p> <p>Gender (M/F) EG1=4M/2F EG2=6M/2F CG=4M/3F</p>	<p>CG –standard arm therapy i.e. repetitive task training</p> <p>+</p> <p>30min therapist-assisted arm mobilization</p> <p>3d/wk.</p>		<p>hand grasping (open and close hand) or knob manipulation (pronation and supination)</p>		<p>EG1 8.2± 2.9 – 6wk 9.7 ±2.9 – 18wk EG2 6.5 ± 4.4 – 6wk 8.3 ± 5.0 –18wk</p> <p>Only EG1 had differences during follow-up compared to CG</p> <p>No differences were observed between EG1 and EG2 and between EG2 and CG</p>
Ang, Guan, et al., 2015	<p>RCT</p> <p>N Total=19 N EG=10 N CG=9</p> <p>Mean age, SD (years) EG=52.1 ±11.7</p>	<p>EG- Real tDCS CG -Sham tDCS during 20min</p> <p>+</p> <p>1 hour EEG-based MI-BCI with robotic feedback</p> <p>4 runs of 40 trials (total 160</p>	2wks(10sessions)	Identical to Ang et al. (Ang, et al., 2010)	<p>FMA</p> <p>Timing: - Pre-test, 2wks after the start of the intervention</p> <p>- Follow-up 2wks</p>	<p>No significant functional gains, after intervention, in both groups.</p> <p>At follow-up both groups improved EG: 5.0±4.4, CG: 5.4±5.7</p>

	<p>CG= 56.3 ± 9.5</p> <p>time post stroke (mths) EG=34.6±23.72 CG=33.5±15.28</p> <p>Type (I/H) EG=6I/4H CG=7I/2H</p> <p>Side (R/L) EG=5R/5L CG=6R/3L</p> <p>Gender (M/F) EG=6M/4F CG=8M/1F</p>	<p>trials)</p> <p>5d/wk.</p>			after post-test	No differences between groups
Frolov, et al., 2017	<p>RCT</p> <p>N Total=74 N EG=55 N CG=19</p> <p>Mean age, SD (years) EG=55.0 ±12.9 CG= 58.5 ± 10.9</p> <p>time post stroke (mths) EG= 8.9±6.4 CG=8.8±8.4</p> <p>Type (I/H) EG=39I/16H CG=16I/3H</p>	<p>30min rehabilitation sessions:</p> <p>EG - BCI-controlled exoskeleton + standard physical therapy: instructor-supervised kinesiotherapy, medical massage, and FES</p> <p>CG – Idem However, Passive Exoskeleton-Driven Movements of the Paretic Hand (Sham Condition)</p>	2wks (10 sessions)	<p>A visual cue on a screen (arrow) instructed subject to perform motor relaxation, MI for both affected and unaffected hand.</p> <p>Visual and Kinaesthetic and proprioceptive feedback: a hand exoskeleton (Neurobotics, Russia) with pneumatic actuators flexed or extended the fingers.</p>	<p>FMA ARAT</p> <p>Timing: - Pre and 2wks after the start of the intervention</p>	<p>Both Groups improved after treatment. However, EG improved more in distal function in Both ARAT and FMA. And had more patients which achieved the MCID</p> <p>EG MCID 21,8% ARAT and 36,4% FMA</p> <p>CG MCID 5,1% ARAT 15,8% FMA</p>

	Side (R/L) EG=29R/26L CG=7R/12L Gender (M/F) EG=34M/11F CG=14M/5F	5d/wk.				
Li, et al., 2014	RCT N Total=14 N EG=7 N CG=7 Mean age, SD (years) EG= 66.3 ±4.89 CG= 67.1±5.95 time post stroke (mths) EG= 2.8±2.31 CG= 1.7 ±1.13 Type (I/H) EG=6I/1H CG=5I/2H Side (R/L/B) EG=4R/1L/2B CG=4R/1L/2B Gender (M/F) EG=5M/2F CG=6M/1F	EG - Conventional therapy 5d/wk. + BCI-based FES (160 trials) 1~1.5h 3d/wk. CG – Conventional therapy 5d/wk. + 20min FES 3d/wk.	8wks(24sessions BCI-FES and 40sessions conventional therapy)	Visual and Kinaesthetic and proprioceptive feedback: FES was triggered and stimulated extensor carpus radialis muscles of the affected upper extremity after correctly imagined the movement five times in succession, i.e. correctly performed 5 games with basic cognition tasks (move eyes, lift a balloon, balance a bean, drink water, navigate a maze).	FMA ARAT Timing: - Pre-test, weekly during 8w of intervention - No Follow-up	Both Groups improved after 8 wks. of treatment EG FMA +12.7 (12.16) ARAT +18.0 (8.47) CG FMA +6.9 (4.63) ARAT +17.6 (8.20) Only in ARAT were significant differences between groups after 6, 7 and 8 wks.

Ramos-Murguialday, et al., 2013	<p>RCT</p> <p>N Total=30 N EG=16 N CG=14</p> <p>Mean age, SD (years) EG=49.3 ±12.5 CG= 50.3 ± 12.2</p> <p>time post stroke (mths) EG=66±45 CG=71±72</p> <p>Type (I/H) NA</p> <p>Side (R/L/B) EG=8R/8L CG=8R/6L</p> <p>Gender (M/F) EG-9M/7F CG-9M/5F</p>	<p>EG – EEG- based MI-BCI orthosis - 275 ± 25(runs; 1run=11trials x 5s) 5d/wk.</p> <p>CG - sham- EEG- based MI-BCI orthosis - 291 ± 17(runs) 5d/wk.</p> <p>+</p> <p>1h of behavioural PT</p>	4wks (20 sessions)	Kinaesthetic and proprioceptive feedback: a mechanical hand orthosis reaching and grasping movements of the hand	<p>modified FMA MAL GAS</p> <p>Timing: - Pre-test 2mths before (Pre1) and immediately before (Pre2), 4wk after the start of the intervention</p> <p>- No Follow-up</p>	<p>CG had no improvement while EG improved function with intervention from 11.16 ± 61.73 to 14.56 ± 61.95.</p> <p>94% EG improved in modified FMA compared to 50% of CG</p>
Jang, et al., 2016	<p>RCT</p> <p>N Total=20 N EG=10 N CG=10</p> <p>Mean age, SD (years) EG= 61.1±13.77 CG= 61.7±12.09</p>	<p>EG – AOT plus BCI-based FES 30min 5d/wk.</p> <p>+</p> <p>OT 20min 5d/wk.</p> <p>CG – FES 30min 5d/wk + OT 20min 5d/wk.</p>	6wks(30sessions)	Visual and Kinaesthetic and proprioceptive feedback: FES was triggered and stimulated supraspinatus and posterior deltoid muscles of the affected muscles of the upper extremity after	<p>VAS MAS MFT</p> <p>Timing: - Pre-test and 4wks after the start of the intervention</p>	<p>Both Groups improved after 6 wks. of treatment</p> <p>EG Total MFT score -7.80±4.26</p> <p>CG Total MFT score -4.90 (4.48)</p>

	time post stroke (mths) EG= 4.4±0.97 CG= 4.1 ±0.74 Type (I/H) EG=6I/4H CG=6I/4H Side (R/L) EG=5R/5L CG=2R/8L Gender (M/F) EG=6M/4F CG=4M/6F			the performance of four shoulder movement sequences (abduction or and adduction with and without weight) by watching a computer monitor screen.	- No Follow-up	EG improved more than CG in two out of eight items of the MFT (shoulder flexion and shoulder abduction)=0.016),
Kim, et al., 2015	RCT N Total=30 N EG=15 N CG=15 Mean age, SD (years) EG= 59.1 ±8.1 CG= 59.9±9.8 time post stroke (mths) EG= 8.3±1.98 CG= 7.8 ±1.78 Type (I/H) EG=8I/7H	EG - AOT plus BCI-based FES 30min 3d/wk. + OT 30min 5d/wk. CG – OT 30min 5d/wk.	4wks(12sessions BCI and 20sessions OT)	Visual and Kinaesthetic and proprioceptive feedback: FES was triggered and stimulated wrist extensor muscles of the affected upper extremity after the performance of 18 action observational training related to their daily living by watching DVDs.	FMA, MAL, MBI, ROM Timing: - Pre-test and 4wks after the start of the intervention - No Follow-up	Both Groups improved after 4 wks. of treatment EG FMA +7.87 (2.42) MAL-AOU +13.07 (7.56) MAL-QOM +9.40 (8.70) CG FMA +2.93 (2.74)

	CG=6I/9H Side (R/L) EG=8R/7L CG=6R/9L Gender (M/F) EG=6M/9F CG=6M/9F					MAL-AOU +5.80 (5.51) MAL-QOM +2.13 (3.23) EG improved more than CG in all outcomes
Mihara, et al., 2013	RCT N Total=20 N EG=10 N CG=10 Mean age, SD (years) EG=56.0 ±7.92 CG= 60.1 ± 8.49 time post stroke (mths) EG=4.8±1.19 CG=4.0±1.26 Type (I/H) EG=5I/5H CG=7I/3H Side (R/L/B) EG=5R/5L CG=3R/7L Gender (M/F)	EG – NIRS- based MI-BCI 3d/wk. CG - sham- NIRS- based MI- BCI 3d/wk. + 180' conventional rehabilitation (60' NDT PT + 60' OT + 60' Speech therapy (if needed)) 7d/wk	2wks (6 sessions)	10' video-guided motor imagery training (16 repetitions of sequential flexion and extension of affected elbow and of sequential folding and unfolding of affected fingers according to the video instruction) followed by 10' kinaesthetic motor imagery training with neurofeedback (real or sham according to EG or CG, respectively).	FMA ARAT MAL Timing: - Pre-test before (Pre) Intervention - Post-test immediately after the end of the intervention (Post1) - Follow-up 2wks after post-test (Post2)	Both Groups improved after 2 wks. of treatment Total FMA score and MAL (amount and quality of paretic arm use) was improved in both group ARAT was not improved in either group EG FMA Post1 +5.7±2.91 Post2 +6.2±3.29 ARAT Post1 +2.3±4.69 Post2 +3.9±5.82 MAL AOU Post1 +0.5±0.64 Post2 +0.6±0.73 MAL QOM Post1 +0.3±0.41 Post2 +0.5±0.51

	EG-8M/2F CG-4M/6F					CG FMA Post1 +2.3±1.77 Post2 +4.2±1.93 ARAT Post1 +1.8±4.63 Post2 +3.9±5.96 MAL AOU Post1 +0.3±0.35 Post2 +0.5±0.36 MAL QOM Post1 +0.3±0.31 Post2 +0.5±0.47
Abbreviations: 9-Hole Peg Test (9-HPT); Action observational training (AOT); Action Research Arm Test (ARAT); Barthel Index(BI); Brain-Computer interface(BCI); Case Series(CS); Constraint Induced Modified Therapy(CIMT); Control Group (CG); Experimental Group (EG); Functional Electric Stimulation (FES); Fugl-Meyer Scale for UE(FMA); Female (F); Functional Electric Stimulation(FES); Goal Attainment Scale(GAS); hours(h); Male (M); Minimal Clinically Important Difference (MCID); Manual Function Test (MFT); Modified Ashworth Scale(MAS); Motor Activity Log(MAL); Motor Activity Log-Activity of Use (MAL-AOU); Motor Activity Log-Quality of Movement (MAL-QOM,); Modified Barthel Index (MBI) ;Motor Imagery(MI); months(mths); National Institute of Health Stroke Scale (NIHSS); Near-infrared spectroscopy (NIRS); Neurodevelopmental techniques (NDT); Occupational therapy(OT); Physical Practice (PP); Physical therapy(PT); Randomized Control Trial(RCT); Repetitive, task specific, practice(RTP); Robotic rehabilitation(RR); Stroke Impact Scale (SIS); Stroke Impairment Assessment Set (SIAS); Transcranial Direct Current Stimulation (tDCS); Timed Up and Go(TUG); weeks (wks.) ; Visual analogue scale (VAS); Wolf Motor Function Test(WMFT); wrist joint range of motion (ROM) ; Not Applicable(nA)						

Participants

In total, 278 participants were included in this systematic review, the majority Asian, with an average age of 56.3 ± 5.5 . The time post-stroke average was 16.2 ± 19.92 months, with a range between 1,7 to 71 months. Patients were moderately to severe impaired in six studies and severely impaired in four (Frolov, et al., 2017; Jang, et al., 2016; Li, et al., 2014; Ramos-Murguialday, et al., 2013), i.e. based on previous studies, patients who were severely impaired scored below 25, while those who were moderately impaired scored between 26 and 50 out of 66 in FMA (Luft, McCombe-Waller, et al., 2004). Overall, men-to-women ratio of 1.96:1, left-to-right side ratio of 1:1.04 and only four patients with bilateral lesions were included. However, the following is based on available data, ischemic-haemorrhagic lesion ratio of 1.48:1. The number of subjects randomized to the BCI training ranged from 10 to 74. Dropout rates varied from 3.8 to 17,4%, not only in BCI but also in control groups, and the main reasons were due to pain (Ang, Chua, et al., 2015; Ang, et al., 2010), seizures (Ang, et al., 2014), allergy to electrode pads (Li, et al., 2014) and discharge (Jang, et al., 2016; Kim, et al., 2015).

Types of BCI and feedback used

Near-infrared spectroscopy (NIRS) based MI-BCI was used in combination with OT and a visual feedback information was displayed in a monitor, in comparison with a sham neurofeedback (Mihara, et al., 2013). The remaining nine studies focused on EEG-based MI-BCI and all used non-invasive scalp EEG-based recordings. Two of which were combined with robotic feedback neurorehabilitation compared to standard robotic rehabilitation (Ang, Chua, et al., 2015; Ang, et al., 2010), while the other included Haptic Knob robotic feedback compared to Haptic Knob robot or standard arm rehabilitation (Ang, et al., 2014). Moreover, three used sham intervention, two studies compared real neurofeedback with sham-EEG-based MI-BCI orthosis (Ramos-Murguialday, et al., 2013) while the other used, in both groups, an EEG-based

MI-BCI robotic feedback however, combined with previous transcranial direct current stimulation (tDCS) in the experimental group or with sham tDCS intervention in the control group, in order to define the clinical efficacy of tDCS real and/or sham on MI-BCI with robotic feedback in stroke patients(Ang, Guan, et al., 2015). The number of trials in two studies was the same between groups(Ang, et al., 2014)(Ang, Guan, et al., 2015), while in the others the number of trials was not matched between the experimental and control groups(Ang, Chua, et al., 2015; Ang, et al., 2010),⁴⁰ or had no reference to it(Frolov, et al., 2017) (see table 2). Finally, three others used EEG-based MI-BCI combined with functional electrical stimulation (FES) and OT(Jang, et al., 2016; Kim, et al., 2015) or physical therapy, exercise therapy and acupuncture therapy(Li, et al., 2014) comparatively to the respective therapies alone (table 2).

Frequency of the intervention varied from three to five times a week, ongoing for two to eight weeks, with a range from 6 to 24 sessions. The duration was quite variable.

Studies associated to visual feedback used different types of kinaesthetic and somatosensory feedback: three studies used a robotic arm supporting the movement of the paretic limb in a forward/backward motion or towards a goal shown on a screen(Ang, Chua, et al., 2015; Ang, et al., 2010; Ang, Guan, et al., 2015); one study used a robot which simulated a hand grasp combined with knob manipulation (pronation-and-supination)(Ang, et al., 2014); two used an orthosis which emulated hand grasping and hand-opening(Ramos-Murguialday, et al., 2013); and three others used the stimulation of wrist extensor muscles(Kim, et al., 2015; Li, et al., 2014) or of the supraspinatus and posterior deltoid muscles(Jang, et al., 2016) of the affected upper extremity through FES, as feedback.

Six studies added BCI training to therapist-assisted arm mobilization(Ang, et al., 2014), to physical therapy, exercise therapy and acupuncture therapy(Li, et al., 2014), to occupational

therapy(Jang, et al., 2016; Kim, et al., 2015), to physical therapy and occupational therapy and speech therapy if needed(Mihara, et al., 2013), to behavioural therapy(Ramos-Murguialday, et al., 2013) or to standard physical therapy, instructor-supervised kinesiotherapy, medical massage, and FES.

Outcome Measurements

The upper limb function was measured before and after intervention in each reviewed study; follow-up data was reported in four studies(Ang, Chua, et al., 2015; Ang, et al., 2010; Ang, Guan, et al., 2015; Ang, et al., 2014). A variety of instruments was used, being the FMA scale common to all studies except one, which used the Manual Function Test (MFT)(Jang, et al., 2016), while others included the Motor Activity Log (MAL)(Li, et al., 2014; Ramos-Murguialday, et al., 2013), the Action Research Arm Test (ARAT)(Li, et al., 2014), the Goal Attainment Scale(GAS)(Ramos-Murguialday, et al., 2013). The wrist joint range of motion (ROM)(Kim, et al., 2015) was also collected.

Effects of BCI training in upper limb function

As shown in the table 2, in Ang and collaborators studies, both control and experimental groups improved upper limb function after intervention(Ang, Chua, et al., 2015; Ang, et al., 2010; Ang, et al., 2014) except in one study which only improved after 2 weeks during the follow-up(Ang, Guan, et al., 2015). Robotic rehabilitation, at short-term, improved functionality more than BCI combined with robotic rehabilitation(Ang, Chua, et al., 2015; Ang, et al., 2010; Ang, et al., 2014) however, during the follow-up in two studies, the increase in upper limb function was higher and kept improving(Ang, Chua, et al., 2015; Ang, et al., 2014) in the BCI groups, nonetheless, no differences were found between groups. The real transcranial direct current stimulation (tDCS) before BCI training has the same efficacy as sham tDCS has(Ang, Guan, et al., 2015), with improvements only during follow-up. There was an increase in arm function in real EEG based

MI-BCI orthosis compared to sham BCI(Ramos-Murguialday, et al., 2013), however in Frolov et al.(2017) study this difference only occurred in distal hand function. BCI combined with FES and conventional or occupational therapy improved comparatively to the therapies alone(Jang, et al., 2016; Kim, et al., 2015; Li, et al., 2014), however the improvement in all outcome measures only occurred in one study(Kim, et al., 2015). The NIRS-based MI-BCI, even during a short period (6 sessions) seems to benefit acute stroke patients compared to a sham intervention(Mihara, et al., 2013).

Discussion

This systematic review included ten studies with high quality research and demonstrated some benefits of BCI in upper limb recovery, which consequently remained after intervention. Besides those mentioned, several other studies with similar purposes have been conducted in stroke patients(Buch et al., 2008; Caria et al., 2011; Prasad, Herman, Coyle, McDonough, & Crosbie, 2010; Varkuti, et al., 2013) and depict some interesting findings. Although some of these tried to select the optimal amount of EEG channels in order to decrease costs and increase specificity and accuracy of rhythm modulation in stroke patients(Tam, Tong, Meng, & Gao, 2011), there were others which tried to define the best way to carry out a reliable detection of motor intention(Ang et al., 2011; Niazi et al., 2011). However, these were not included since they did not satisfy our objective or had enough quality based on PEDro scale.

Intervention characteristics and its results

Overall, studies involving a BCI-system in combination with physical therapy to promote recovery after stroke suggest a benefit of this approach over conventional or occupational therapy(Kim, et al., 2015; Li, et al., 2014) or in robotic rehabilitation(Ang, Chua, et al., 2015; Ang, et al., 2010; Ang, et al., 2014; Frolov, et al., 2017; Ramos-Murguialday, et al., 2013). Similarly, other studies(Caria, et al., 2011; Li, et al., 2014; Prasad, et al., 2010) mention good results not only in

functionality but also in terms of normalization of brain activation patterns(Caria, et al., 2011). Interestingly, when comparing standard robotic rehabilitation with EEG-based BCI system with robotic feedback(Ang, Chua, et al., 2015; Ang, et al., 2010), the average motor improvement found in the experimental group was slightly less than in controls. While the authors suggested that this could be due to the limited number of intervention trials, the heterogeneity of lesion sites, age and time post stroke are also likely contributors. Yet, in follow-up, this seems to reverse, suggesting that BCI had more long-term changes/results. The recovery observed can either be the result of a more “normal” brain activation, in terms of lateralization, induced by the central nerve system guided through BCI or the contingent sensory input given by feedback, which increases the synaptic strengthening of reduced or previously inhibited motor networks(Ono, et al., 2014; Soekadar, et al., 2015). Recently(Varkuti, et al., 2013), an improvement was described in neuroplasticity and function in both the BCI and control groups (robotic rehabilitation), though higher (and more variable) in the former. The authors interpreted these findings thus suggesting that BCI training strengthens neuroplasticity, which leads to better recovery. However, care must be considered because of the small sample size. Nevertheless, there were no differences in functional gains, immediately after intervention, when comparing the exclusive use of Haptic Knob robot or if it was allied to EEG-based MI-BCI(Ang, et al., 2014), but longer proprioceptive feedback intervention seems to benefit patients more compared to intensive training with visual feedback(Ono, et al., 2014).

Additionally, more updated literature stated that when relating the combination of real tDCS(Ang, Guan, et al., 2015; Kasashima-Shindo, et al., 2015) or sham(Ang, Guan, et al., 2015) with 1 hour EEG-based MI-BCI to a robotic feedback, both groups improved functionality near the MCID of FMA. Yet, the accuracy in controlling BCI was higher in the former(Ang, Guan, et al., 2015; Kasashima-Shindo, et al., 2015), probably due to changes in brain activity(Kasashima-Shindo, et

al., 2015). Similar results occurred in a NIRS-based MI-BCI intervention when compared real to sham neurofeedback(Mihara, et al., 2013). Though not a clinical trial, a case report(Caria, et al., 2011) raised an interesting question on the comparative efficacy of EEG and MEG based systems. The authors described a chronic stroke male patient who underwent 4-weeks of MEG-based BCI system followed by a 4-week EEG-based BCI system (20 sessions each) combined with physical therapy (1h/day). Neurofeedback was provided visually in combination with opening/closing of an orthosis in the case of MEG and a forward and backward movement of an arm robot in EEG. Following intervention, the patient improved upper limb function and the fMRI data showed an increased lateralization toward the ipsilesional sensorimotor regions; however, there was greater BCI performance after MEG compared to EEG training (assessed by the success in producing the requested mu rhythm amplitude modulation). These results can be related to motivation in the initial sessions compared to the final ones or to the kinaesthetic and proprioceptive feedback given (hand opening/closing compared to reaching movement). Nevertheless, functional recovery only demonstrated superior to MCID after 8-weeks therefore, the product of this single case can raise issues for further study not only in terms of feedback used but also in the duration of the intervention necessary to induce recovery.

In summary, the studies with BCI suggest that patients with chronic or acute stroke had the accuracy to perform MI with feedback (visual, kinaesthetic and/or proprioceptive) even though volitional isolated finger movement was not possible. Nonetheless, there is no clear evidence that a BCI system does in fact improve the motor function of severe stroke patients(Buch, et al., 2008; Ramos-Murguialday, et al., 2013). On the other hand, training with an EEG or MEG BCI system may cause neuroplasticity. However, conclusions regarding functional recovery must be carefully taken into consideration, given the mentioned limitations of the studies and patient characteristics(Buch, et al., 2008; Caria, et al., 2011; Prasad, et al., 2010). Recently, Soekadar

and colleagues(2015) referred to several studies with BCI in stroke neurorehabilitation and reinforced the idea to confirm results through larger clinical trials and mentioned the difficulty in assessing data due to the heterogeneity in clinical tests.

Neurofeedback

As observed, the most popular BCI systems used in stroke rehabilitation are based on EEG, and feedback is usually visual or a combination of visual feedback with the control of an orthosis/robotic limb(Ang, Chua, et al., 2015; Ang, et al., 2010; Ang, Guan, et al., 2015; Ang, et al., 2014; Frolov, et al., 2017; Ramos-Murguialday, et al., 2013). However, a NIRS- based MI-BCI with only visual feedback was also included(Mihara, et al., 2013). Similarly, several other studies, not selected for this review, mentioned an orthosis which emulates hand grasping and hand-opening(Buch, et al., 2008; Caria, et al., 2011; Kasashima-Shindo, et al., 2015; Ono, et al., 2014; Shindo et al., 2011) or a robotic arm supporting the movement of the paretic limb in a forward and backward motion(Caria, et al., 2011) or conducting it towards a goal shown on a screen(Varkuti, et al., 2013). This type of feedback offers important kinaesthetic information with subsequent motor performance guidance, similar to what happened in MI studies where repetitive physical practice coupled with MI induced larger cortical changes, hence leading to cortical reorganization and functional outcome improvement(Butler & Page, 2006) at least, with short-term effects.

Regarding visual feedback, the one used in the present review is predominantly abstract, contrary to others which have included realistic visual feedback(Cincotti, et al., 2012; Neuper, Scherer, Wriessnegger, & Pfurtscheller, 2009; Ono, et al., 2014; Pichiorri, et al., 2015). Realistic feedback, such as a virtual hand movement, might be preferable to more abstract feedback, given the possibility that observation of the virtual hand movement may itself lead to an activation of mirror neuron in the sensorimotor areas(Lucca, 2009; Pfurtscheller, Muller-Putz, Scherer, &

Neuper, 2008). Indeed, Arya and collaborators(2011) show that an enriched training environment, including the use of realistic feedback, helps stimulate cortical reorganization and motor/functional recovery. However, according to Neuper et al.(2009), feedback type per se (whether realistic or more abstract) does not influence the performance in BCI applications, at least in healthy subjects. Nonetheless, Prasad and colleagues(Prasad, et al., 2010), demonstrated that not only did patients improve in at least one functional outcome measure, but also found a correlation between functional improvement (assessed by the ARAT) and the individual ability to control brain activity, whenever visual neurofeedback was provided as part of a computer game (abstract). Nonetheless, this study was the first to relate non-robotic rehabilitation with BCI. Regrettably, the relevance of the findings was limited due to the lack of a control group. Recently, when BCI was compared to MI alone, both allied to an intensive therapy, significant improvement in the former was found in upper limb function(Pichiorri, et al., 2015). Interestingly, BCI training demonstrated greater desynchronization in the sensorimotor rhythms involving the mesial area and the postcentral regions of the ipsilesional hemisphere. Therefore, since visual feedback may interfere positively or negatively with the rehabilitation process, studies should be performed in order to verify if realistic visual feedback combined with robotic feedback in stroke patients could improve upper limb function even more.

Despite patients showing functional gains related to the feedback produced by muscle stimulation guided through BCI and FES(Kim, et al., 2015; Li, et al., 2014), it is unclear whether the gains derived from BCI, FES, the combination of both or simply from whole arm or hand motor task practice similar to previous studies(Daly et al., 2009). Although some doubts concerning FES remain, when comparing it with or without BCI, the former did increase in both hand function (in one of two outcome measures) and MI performance in the acute phase. However, no differences were found in brain symmetry between groups(Li, et al., 2014; Ono, et

al., 2014). Contrarily, changes in functional connectivity occurred when feedback through FES was combined with an attempted movement, which can be related with the thalamocortical circuits and/or the appropriate cortical activity encouraged by BCI (see Young, Nigogosyan, Remsik, et al., 2014; Young, Nigogosyan, Walton, et al., 2014).

Patient characteristics

The characteristics of patients can interfere with the accuracy to control a BCI. The patients in the above mentioned studies were relatively young compared to those across European countries(Heuschmann et al., 2009), with a time post-stroke quite variable which led to difficulty in defining the best period to apply BCI training. Since fatigue can be an issue in the acute phase(Miller et al., 2013; Soekadar, et al., 2015), and MI, used in BCI control, demands great amount of attention, can justify the similarity between BCI with robotic rehabilitation at short time (Ang et al., 2010; Ang, Chua, et al., 2015; Frolov, et al., 2017) and the improvement in the follow-up (Ang, Chua, et al., 2015). Importantly, studies depict that, independently of the feedback given, patients (acute or chronic) can effectively control a BCI system(Ang, Chua, et al., 2015; Ang, et al., 2010).

Regarding severity, the study(Ramos-Murguialday, et al., 2013), which was carried out, involved severely impaired subjects and a homogeneous sample (i.e., the experimental and sham groups were matched by age, gender, paretic side, and motor impairment scores). Both these groups had a similar amount of BCI training and showed a significant improvement in hand function, but the intervention group had higher muscle activity. Of note, the authors(Ramos-Murguialday, et al., 2013) considered the average gain of 3.4 points on the modified FMA in the experimental group as clinically significant, in line with a significant change in the same limb from none to some muscle activity. However, if one considers 5.2 points as the minimal clinically meaningful change in the FMA(Wagner, Rhodes, & Patten, 2008), as previously determined in chronic stroke

patients, this outcome must be considered with caution. Similarly, Shindo and collaborators observed improvement in both finger function and surface EMG activity of the affected finger extensors, even in patients with little or no motor function(Shindo, et al., 2011). Nevertheless, other studies have reported negative findings. One of which recruited chronic stroke patients with hand plegia, and used a MEG-based BCI system to modulate the mu rhythm, with visual feedback and the opening/closing of an orthosis attached to the impaired hand(Buch, et al., 2008), and showed no functional recovery, even in patients who became very proficient in manipulating the orthosis with the BCI. Regardless of these results, this study was the first to suggest that stroke patients with complete hand paralysis can learn to control a MEG-based BCI system. Moreover, recently Frolov and collaborators(2017) demonstrated gains above minimal clinical important differences in distal hand function in BCI group compared to sham group in severe patients, suggesting that BCI could be a strategy in rehabilitation of stroke patients.

The ischemic-haemorrhagic ratio in these studies was also different from that of European countries; consequently, care must be taken in some conclusions. Additionally, the majority of patients(Ang, et al., 2010; Ang, Guan, et al., 2015; Ang, et al., 2014; Kasashima-Shindo, et al., 2015; Li, et al., 2014; Nilsen, et al., 2010) had subcortical stroke, leaving the cortical circuits intact, thus the ability to produce MI was better(Luft, Waller, et al., 2004) and could also interfere with the capacity to control a BCI system. Ramos and collaborators(Ramos-Murguialday, et al., 2013) explored the cortical activity with fMRI/EEG and found an increased activity in ipsilesional cortical areas during the motor execution task in the experimental group, nevertheless this might be due to the different proportion of subcortical stroke (14/16 vs 7/16, experimental vs sham respectively). However, one question remains and may be interesting for future study: do patients still have the same results in cortical stroke?

Though patients had neither cognitive impairment nor the inability to control BCI, recent studies suggest patients who have mild cognitive disability(Niazi, et al., 2011), can also control BCI devices. Moreover, BCI-based training of the unaffected side(Bundy et al., 2012) can also help restore limb function contralaterally, providing hope to those patients with severe stroke, and who might not have been able to control BCI when using the affected hemisphere. This suggests that BCI can also be an inclusive rehabilitation strategy in the future.

Conclusion

Although there is evidence showing that BCI-based neurofeedback together with physical practice (conventional therapy or robots) can enhance upper limb function recovery, it is still unclear how it promotes clinical and neurophysiological changes in stroke patients in the long-term. Therefore, more and larger studies must be carried out in order to understand if the source of motor recovery derives from conventional therapy, MI, neurofeedback from BCI or the combination of these.

Implication section and hints for the future

As BCI and neurofeedback show promise in the rehabilitation of stroke subjects, more and higher quality research is needed in order to elucidate its effects and discriminate which protocols lead to best results. In order to achieve this goal, studies should be standardized and methodologies clearly described. Hereafter, we provide some suggestions on the design of future studies regarding this topic.

Starting with inclusion criteria, several aspects need to be taken into account such as the characteristics of each patient(Dickstein & Deutsch, 2007) which can interfere with the ability to perform a correct MI and consequently to control a BCI system. Studies should begin with the assessment of MI ability(Sharma & Baron, 2013) beyond the accuracy to control a BCI, since

many patients who are being left out of research, can probably with training reach sufficient accuracy to induce improvement in upper limb function. A similar proportion of male/female participants in each group(Schaechter & Perdue, 2008; Schuster et al., 2011) and a good stratification regarding age is also critical(Saimpont, et al., 2009). The same care should be taken regarding lesion location and handedness(Carey & Seitz, 2007; Ward, Swayne, & Newton, 2008).

The time post stroke should also be considered when testing the impact of a new intervention. In our opinion, to avoid any probability of spontaneous recovery, which occurs in an acute phase, to minimize variability, chronic stroke patients, are preferred, whenever possible(Calautti & Baron, 2003; Rossini, Calautti, Pauri, & Baron, 2003; Small, Hlustik, Noll, Genovese, & Solodkin, 2002). Importantly, time post-stroke has a strong influence not only on functional assessment but also on fMRI and EEG. Additionally, fatigue(Miller, et al., 2013; Prasad, et al., 2010) is less of a problem in chronic phases, therefore reducing the interference with the ability to use a BCI system.

Regarding feedback, one should also bear in mind that the correctness of the classification algorithms has a strong impact on BCI performance. Of note, this impact seems to be non-trivial, since inaccurate feedback might result in weaker performance in healthy subjects who previously had good accuracy, while feedback distortion improves the accuracy of those who perform around chance-level(Barbero & Grosse-Wentrup, 2010). While future studies should try to address which feedback modalities might produce better results, patient preferences for different feedback strategies should also be taken into account. Ideally, feedback should be tailored to the individual, considering personal preferences, but also daily needs and difficulties. By addressing each patient's problems, this strategy will greatly contribute to patient motivation leading to enhanced results.

In order to understand the effect of BCI, we suggest a study with randomization into four groups, i) control (no intervention, to serve as reference to longitudinal fMRI changes due to learning), ii) only conventional therapy (to analyse therapy influence) iii) conventional therapy with simultaneous real neurofeedback and, iv) conventional therapy with sham neurofeedback. In this manner, researchers can conclude if improvement derives from conventional therapy, real neurofeedback or MI itself.

Future studies will help to elucidate which MI-BCI modalities work best and allow the design of more tailored interventions.

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Supplementary tables

Table A.1: Areas of correlation between BOLD and BSI at mu and beta frequency during MER and during MIR

BSI frequency	Task	Cluster Size	T/F-Stat	X (mm)	y (mm)	z (mm)	Location		Rho
							ROI	Side	
Beta	MER	1708	22.00117	-56	-16	40			
			7.390313	-54	-34	54	PostCentral	L	0.87
			7.355099	-56	-20	20			
		2980	12.13412	44	-12	50	PreCentral		
			9.204162	24	-40	74	PostCentral	R	0.79
			7.271595	12	-56	74			
		324	8.236141	-28	-10	-8			
			6.513629	-28	-18	6	Putamen	L	0.67
			5.008533	-26	-2	14			
		294	6.356755	2	8	60			
			4.69698	0	6	72	SMA	L&R	0.78
			4.607984	-2	24	58			
	MIR	160	4.783949	8	-18	14			
			4.131324	16	-20	6	Thalamus	R	0.62
			4.052742	14	-14	-2			
		3858	11.59485912	12	-48	72	PostCentral		
			10.80781174	38	-8	50	PreCentral	R	0.90
			9.946130753	12	8	52	SMA		
		485	9.366578102	-44	0	46	PreCentral		
			7.706522942	-52	6	30	PreCentral	L	0.84
			6.579128265	-58	-6	40	PostCentral		
		312	9.222994804	-22	-54	72	Parietal_Superior		
			5.967674255	-36	-60	62	Parietal_Superior	L	0.84
			5.311644554	-50	-36	60	PostCentral		
mu	MER	—	—	—	—	—	—		—
	MIR	196	7,072102	42	-4	36			
			6,861044	44	-10	44	PreCentral	R	0.84
			6,161219	52	-14	58			

Table A.2: Areas of correlation between BOLD and BSI at mu and beta frequency during MEL and during MIL

BSI frequency	Task	Cluster Size	T/F-Stat	X (mm)	y (mm)	z (mm)	Location		Rho
							ROI	Side	
Beta	MEL	—	—	—	—	—	—	—	—
			16,74889	-10	16	62			
		865	6,72183	-8	24	50	SMA	L	-0,61
			5,660419	-14	8	62			
	MIL		9,259912	22	-70	64			
		823	6,4533	36	-66	58	Parietal_Superior	R	-0,59
Mu			5,562228	16	-76	58			
			9,933661	50	-18	46	PreCentral		
	MEL	229	6,249157	52	-12	56	PreCentral	R	-0.72
			5,454093	62	-12	44	PostCentral		
	MIL	—	—	—	—	—	—	—	—

Annex III

Informed Consent

Colar etiqueta com o número de caso

Consentimento Informado

Caro paciente,

Convidamo-lo a participar num estudo sobre intervenção na função do membro superior em pacientes com acidente vascular cerebral (AVC), cujo título do projecto de investigação é “Neuroplasticidade: como potencializar as intervenções em pacientes com AVC crónico- Conceito de Bobath e Brain-computer Interface”, sendo este coordenado pelo Prof. Doutor João Cerqueira, neurologista no Hospital de São Marcos e no Instituto de Investigação em Ciências da Vida e da Saúde (ICVS) da Escola de Ciências da Saúde da Universidade do Minho. Para qualquer esclarecimento que julgue necessário, pode fazê-lo através de:

Raquel Carvalho

R. Central de Gandra, 1317 4585-116 Gandra, Paredes

raquel.carvalho@ipsn.cespu.pt

Telefone: 224157100

Telemóvel: 917430552

O objectivo deste estudo é verificar a eficácia da fisioterapia segundo o conceito de Bobath na neuroplasticidade e na função do membro superior em pacientes com AVC crónico e atestar a eficácia de um sistema de eletroencefalografia (EEG-based BCI system) associado à fisioterapia segundo o conceito de Bobath na neuroplasticidade e na função do membro superior em pacientes com AVC crónico.

Caso concorde em participar neste estudo, devidamente autorizado pela comissão de ética do seu hospital, fica desde já a saber que a atribuição do grupo a que pertencerá será aleatória podendo estar num grupo onde efectuará apenas fisioterapia ou num grupo que para além da fisioterapia será sujeito ao sistema de electroencefalograma (EEG-based BCI system). O período de intervenção do estudo irá decorrer durante um mês com sessões diárias de fisioterapia e, caso seja o seu caso, associadas ainda sessões de EEG-based BCI system três vezes por semana. Estas últimas irão consistir numa tarefa que implica o treino de um movimento imaginado de uma actividade do dia-a-dia, controlada por EEG. Será fornecido um neurofeedback visual a partir da leitura do seu EEG em tempo real ou será fornecido a partir de dados de outros pacientes (sham). Torna-se pertinente a participação em todas as sessões planeadas quer de fisioterapia quer de EEG-based BCI system. O EEG-based BCI system é um método não-invasivo, basicamente inofensivo, podendo causar desconforto a colocação e remoção dos eléctrodos, contudo é a única forma de controlar a atenção durante a prática do movimento imaginado.

As avaliações das modificações que ocorrem em termos de neuroplasticidade serão efectuadas através da ressonância magnética funcional (fMRN), sendo necessária a realização de uma antes e outra depois da

intervenção. O grupo que apenas realizará fisioterapia, de modo a se tentar provar o efeito da mesma na reabilitação terá de fazer, mais uma fMRN, estando um mês sem ser sujeito a qualquer tipo de intervenção fisioterapêutica. Para a avaliação funcional do membro superior utilizar-se-ão os seguintes testes: Action research arm test, Motor assessment scale, Fugl-Meyer assessment scale – arm section, Rivermead Motor Assessment upper-limb scale. Estas avaliações serão filmadas para posterior avaliação. As medidas de avaliação da função tratam-se de testes clínicos que não trazem nenhum desconforto aos pacientes e a fMRN é um método não-invasivo e não induz nenhuma exposição a radiação.

Espera-se que este tipo de intervenção, fisioterapia segundo o conceito de Bobath, assim como a prática do movimento imaginado, traga benefícios em termos de função motora do membro superior e sem risco adicional em pacientes com AVC.

Os incómodos derivados da participação são: o tempo despendido em deslocações para as sessões de intervenção (45 minutos diários de fisioterapia e 20 minutos 3 vezes por semana no caso do EEG) e de avaliação (2 ou 3 sessões, para avaliação da função do membro superior, RMN e EEG); o desconforto que possa surgir na colocação e na remoção dos eléctrodos para realização da EEG; o desconforto devido ao ruído durante a Ressonância Magnética.

Os seus dados clínicos e os dados dos exames e testes, serão conservados, em condições adequadas e sem elementos que o permitam identificar, nas instalações do Instituto de Investigação em Ciências da Vida e da Saúde da Universidade do Minho e poderão ser utilizados, de forma anónima, noutros estudos, exclusivamente com fins de investigação, desde que devidamente autorizados por uma Comissão de Ética.

Caso prefira não participar, os procedimentos diagnósticos e terapêuticos devidos à sua situação actual não serão minimamente afectados e continuará a ser seguido pelo seu neurologista assistente, sendo-lhe igualmente oferecido, de acordo com o seu diagnóstico, um programa de vigilância adequado. Se tiver alguma dúvida em relação a este estudo, por favor coloque-a ao seu médico assistente até ficar completamente esclarecido.

Se necessitar tem tempo disponível para reflectir sobre o pedido de participação (1 mês), inclusive poder ouvir opinião de familiares e/ou amigos.

Muito obrigado pela sua atenção!

Raquel Carvalho

(investigador responsável)

DECLARAÇÃO DE CONSENTIMENTO

Considerando a “Declaração de Helsínquia” da Associação Médica Mundial

(Helsínquia 1964; Tóquio 1975; Veneza 1983; Hong Kong 1989; Somerset West 1996 e Edimburgo 2000)

Designação do Estudo (em português):

“Neuroplasticidade: como potencializar as intervenções em pacientes com AVC crónico- Conceito de Bobath e Brain-computer Interface”

Eu, abaixo-assinado, (nome completo do doente ou voluntário são)

, compreendi a explicação que me foi fornecida acerca do meu caso clínico e da investigação que se tenciona realizar, bem como deste único estudo em que serei incluído. Foi-me dada oportunidade de fazer as perguntas que julguei necessárias, e de todas obtive resposta satisfatória.

Tomei conhecimento de que, de acordo com as recomendações da Declaração de Helsínquia, a informação ou explicação que me foi prestada versou os objectivos, os métodos, os benefícios previstos, os riscos potenciais e o eventual desconforto. Além disso, foi-me afirmado que tenho o direito de recusar a todo o tempo a minha participação no estudo, sem que isso possa ter como efeito qualquer prejuízo na assistência que me é prestada.

Declaro também que aceito participar no mesmo estudo, autorizando a recolha de dados sobre a minha situação clínica actual, a realização de ressonância magnética funcional, a filmagem das avaliações funcionais do membro superior, a realização de intervenção de fisioterapia assim como de possível EEG-based BCI system podendo este ser sham, bem como a sua utilização futura, exclusivamente para fins de investigação.

Declaro ainda que fui informado da pertinência da participação em todas as sessões planeadas quer de fisioterapia quer de EEG-based BCI system.

Por isso, consinto que me seja aplicado o método, o tratamento ou o inquérito proposto pelo investigador.

Data: ____ / ____ / 201__

Assinatura do doente ou voluntário são: _____

O Investigador responsável:

Nome: _____

Assinatura: _____

ACEITAÇÃO

Designação do Estudo (em português):

“Neuroplasticidade: como potencializar as intervenções em pacientes com AVC crónico- Conceito de Bobath e Brain-computer Interface”

Eu, abaixo-assinado, (nome completo do doente ou voluntário são) _____, declaro que fui informado do estudo sobre a intervenção na função do membro superior em pacientes com acidente vascular cerebral pelo Dr _____, que respondeu a todas as minhas questões.

Declaro também que aceito participar no mesmo estudo, autorizando a recolha de dados sobre a minha situação clínica actual, a realização de ressonância magnética funcional, a filmagem das avaliações funcionais do membro superior, a realização de intervenção de fisioterapia assim como de possível EEG-based BCI system podendo este ser sham, bem como a sua utilização futura, exclusivamente para fins de investigação.

Declaro ainda que fui informado da pertinência da participação em todas as sessões planeadas quer de fisioterapia quer de EEG-based BCI system.

Data: ____ / ____ / 201____

Assinatura do doente ou voluntário são: _____

O Médico:

Nome: _____

Assinatura: _____

Annex IV

Registration

Folha de informações

Colar etiqueta com o número de caso

1. Identificação do doente

Colar uma etiqueta do doente ou indicar nome, idade, género e nº de processo, por favor.

Escolaridade: Ler/escrever ☐ 1º Ciclo ☐ 2º Ciclo ☐ Secundário ☐ Ensino Superior ☐

2. Dados sobre a recolha de informação

Data: _____ Hora: _____ Local: _____

3. Informação clínica breve

Data do AVC: ____/____/____

Tipo de AVC: ☐ Isquémico ☐ Hemorrágico*

Lado do AVC: ☐ Esquerdo ☐ Direito*

Lesões Encefálicas: ☐ Corticais (coroa radiada e córtex motor) ☐ Subcorticais (áreas mediais do córtex insular, região ventral do corpo caloso, núcleos da base, cápsula interna, pedúnculos e vias descendentes) ☐ corticais e subcorticais

Outro tipo de lesões e sequelas:

☐ Tumor cerebral*; ☐ Cirurgia cerebral*; ☐ Outras co morbilidades:
Qual/quais? _____

☐ História de epilepsia prévia ao AVC*; ☐ Insuficiência cardíaca que interfira com o exercício físico;

☐ Claustrofobia;

☐ Drogas psicotrópicas:
Qual/quais? _____

☐ Défices auditivos e visuais não compensados*

☐ Afasia; O paciente é: ☐ Incapaz de compreender o que lhe é dito*, ☐ Incapaz de ler*, ☐
Incapaz de escrever linguagem compreensível*, ☐ Exibe fala parafásica fluente *

☐ Deterioração cognitiva ou demência*. Classificação segundo Mini mental State Exam (valores de cutoff: 15 para iletrados, 22 para 1-11 anos de escolaridade e 27 para 12 ou mais anos de escolaridade) se aplicável _____

☐ Depressão; Medicação: _____

☐ Fenómenos de anosognosia ou negligência, amnésia

☐ Espasticidade severa, (MAS $\geq 3^*$). Classificação segundo Escala Modificada de Ashworth (MAS) se aplicável _____

☐ Dor que possa restringir o movimento do membro superior ($EVA \geq 4^*$). Classificação EVA se aplicável_____

4. Nome do Observador e n° da ordem

Muito obrigado!

Raquel Carvalho

* Critério de exclusão

LVIII

Annex V

Questions related to EEG and fMRI application viability

INFORMAÇÃO RELATIVA AO EXAME DE ENCEFALOGRAFIA (EEG)

O EEG é um exame que permite estudar as correntes elétricas do seu cérebro e é a única forma de controlar a atenção durante a prática do movimento imaginado.

O EEG é um método não-invasivo e inofensivo, em que se encostam elétrodos ao couro cabeludo para registar a atividade elétrica cerebral, pode eventualmente causar desconforto a colocação e remoção dos elétrodo.

O exame tem duas sessões e cada sessão dura aproximadamente 20 minutos.

É importante para a qualidade das imagens que se mantenha calmo e atento.

Se sentir desconforto poderá a qualquer altura chamar o investigador (que o acompanha durante todo o processo).

Devido a algumas interferências na qualidade do sinal, é importante que nos diga se teve, ou tem, algum dos seguintes:

	Sim	Não
Aparelho auditivo		
Problemas visuais		
Se sim, qual(ais)? _____		
História de epilepsia prévia ao AVC		
É a primeira vez que faz exame de EEG?		

Data: _____

Assinatura do próprio ou do representante legal: _____

Assinatura do investigador responsável: _____

QUESTIONÁRIO DE SEGURANÇA PARA EXAME DE RESSONÂNCIA MAGNÉTICA (RM)

A RM é um exame que permite estudar o corpo humano sem o uso de radiação ionizante, através de um poderoso íman.

A RM não tem efeitos secundários conhecidos.

Não provoca qualquer tipo de dor e, irá realizá-lo confortavelmente deitado. Através de um espelho conseguirá ver o que lhe é pedido para realizar.

Durante o processo irá ouvir ruídos que nos dizem que o exame está a ser feito, ou seja, que as imagens estão a ser formadas.

O exame tem duas sessões e cada sessão dura aproximadamente 30 minutos.

É importante para a qualidade das imagens que se mantenha calmo e imóvel.

Se sentir desconforto poderá a qualquer altura chamar o técnico (que o acompanha durante todo o processo) através de uma campainha que fica no seu colo.

Durante os períodos de repouso deve tentar evitar fechar os olhos, fixar a seta com o olhar e não pensar em mais nada.

Devido ao campo magnético utilizado, é importante que nos diga se teve, ou tem, algum dos seguintes:

	Sim	Não
Próteses		
Implantes		
Pacemaker ou válvulas cardíacas		
Clipes cerebrais		
Pedaços de ferro ou outros materiais metálicos no corpo		
Aparelho auditivo		
Placa dentária, material de ortodontia, implantes dentários		
Já fez alguma cirurgia?		
A quê e quando? _____		
Sofre de claustrofobia (medo de espaços muito pequenos)?		
Já foi maquinista, serralheiro, soldador ou trabalhou com metais?		
Já foi alvejado / baleado?		
Poderá estar grávida?		
É a primeira vez que faz exame de RM?		

Data: _____

Assinatura do próprio ou do representante legal _____

Assinatura do investigador responsável: _____

Annex VI

Assessment Scales

Folha de informações

Colar etiqueta com o número de caso

1. Identificação do doente

Colar uma etiqueta do doente ou indicar nome, idade, género e nº de processo, por favor.

2. Dados sobre a recolha de informação

Data: _____ Hora: _____ Local: _____

Escolaridade: Ler/escrever ☐ 1º ciclo ☐ 2º Ciclo ☐ Secundário ☐ Ensino Superior ☐

3. Avaliação:

Classificação segundo MMSE _____

Classificação segundo MOCA _____

Classificação EVA se aplicável _____

Registo avaliação do Membro superior

	Avaliação	Reavaliação (Data)
Instrumentos de Medida	Classificação (Data)	Classificação (Data)
Escala Modificada de Ashworth (MAS) Flexores /Extensores (se aplicável)		
Lateralidade - Edinburgh Handedness Inventory – antes do AVC		_____
Action research arm test		
Motor assessment scale - Membro superior		
Fugl-Meyer assessment scale – arm section		

Instrumentos de avaliação clínica

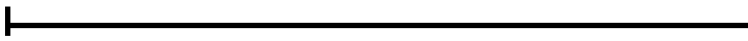
Lateralidade - Edinburgh Handedness Inventory – antes do AVC

	Esquerda	Direita	
1. Escrever			Pontuação: Somar o número de vistos nas colunas da "esquerda" e da "direita" e introduza na linha "TOTAL" para cada coluna. Some o total da esquerda e o total da direita e introduza no "TOTAL acumulativo". Subtraia o total da esquerda com o total da direita e entrar na célula da "diferença". Divida a "diferença" pelo "TOTAL acumulativo" (arredonde a 2 dígitos, se necessário) e multiplique por 100; digite o resultado no "Resultado". (Diferença / Total acumulativo X 100 = Resultado)
2. Desenhar			
3. Atirar			
4. Tesoura			
5. Escova de dentes			
6. Faca (sem garfo)			
7. Colher			
8. Varrer (mão superior)			
9. Acender um fósforo (fósforo)			
10. Abrir uma caixa (tampa)			
Total			

Interpretação (com base no resultado):

☐ abaixo de -40 = esquerdino ☐ entre -40 e +40 = ambidestro ☐ acima de 40 = destro

Escala Visual Analógica - Avaliação da dor



Escala Modificada de Ashworth (MAS) Flexores /Extensores (se aplicável)

Usada na avaliação da gravidade da espasticidade, varia de 0 a 4:

- 0 - nenhum aumento no tônus muscular;
- 1 - Leve aumento do tônus muscular, manifestado por uma tensão momentânea ou por resistência mínima, no final da amplitude de movimento articular (ADM), quando a região é movida em flexão ou extensão;
- 1+ - Leve aumento do tônus muscular, manifestado por tensão abrupta, seguida de resistência mínima em menos da metade da ADM restante;
- 2 - Aumento mais marcante do tônus muscular, durante a maior parte da ADM, mas a região é movida facilmente;
- 3 - Considerável aumento do tônus muscular, o movimento passivo é difícil;
- 4 - Parte afetada rígida em flexão ou extensão

Mini Mental State Exam

MINI-MENTAL STATE - MMS

NOME: _____

IDADE: _____ Anos

DATA: _____ de _____ de _____

1. ORIENTAÇÃO (1 ponto por cada resposta correcta).

Em que ano estamos? _____
Em que mês estamos? _____
Em que dia do mês estamos? _____
Em que dia da semana estamos? _____
Em que estação do ano estamos? _____
Em que país estamos? _____
Em que distrito vive? _____
Em que terra vive? _____
Em que casa estamos? _____
Em que andar estamos? _____

Nota: _____

2. RETENÇÃO (contar 1 ponto por cada palavra correctamente repetida).

"Vou dizer três palavras; queria que as repetisse, mas só depois de eu as dizer todas; procure ficar a sabê-las de cór".

Pêra _____
Gato _____
Bola _____

Nota: _____

3. ATENÇÃO E CÁLCULO (1 ponto por cada resposta correcta. Se der uma errada mas depois continuar a subtrair bem, consideram-se as seguintes como correctas. Parar ao fim de 5 respostas.)

"Agora peço-lhe que me diga quantos são 30 menos 3 e depois ao número encontrado volta a tirar 3 e repete assim até eu lhe dizer para parar".

27 _ 24 _ 21 _ 18 _ 15 _

Nota: _____

4. EVOCAÇÃO (1 ponto por cada resposta correcta.)

"Veja se consegue dizer as três palavras que pedi há pouco para decorar".

Pêra _____
Gato _____
Bola _____

Nota: _____

5. LINGUAGEM (1 ponto por cada resposta correcta).

a. "Como se chama isto? Mostrar os objectos:

Relógio _____
Lápis _____

Nota: _____

b. "Repita a frase que eu vou dizer: O RATO ROEU A ROLHA"

Nota: _____

c. "Quando eu lhe der esta folha de papel, pegue nela com a mão direita, dobre-a ao meio e ponha sobre a mesa", (ou "sobre a cama", se for o caso); dar a folha segurando com as duas mãos.

Pega com a mão direita _____
Dobra ao meio _____
Coloca onde deve _____

Nota: _____

d. "Leia o que está neste cartão e faça o que lá diz". Mostrar um cartão com a frase bem legível, "FECHE OS OLHOS"; sendo analfabeto ler-se a frase.

Fechou os olhos

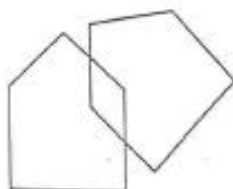
Nota: _____

e. "Escreva uma frase inteira aqui". Deve ter sujeito e verbo e fazer sentido; os erros gramaticais não prejudicam a pontuação.

Nota: _____

6. **HABILIDADE CONSTRUTIVA** (1 ponto pela cópia correcta.)
Deve copiar um desenho. Dois pentágonos parcialmente sobrepostos; cada um deve ficar com 5 lados, dois dos quais intersectados. Não valorizar, tremor ou rotação.

DESENHO



CÓPIA

(Máximo 30 pontos)

TOTAL:

Pontos de Corte (População Portuguesa)

Considera-se com Defeito Cognitivo:

- Analfabetos ≤ 15
- 1 a 11 anos de escolaridade ≤ 22
- Com escolaridade superior a 11 anos ≤ 27

FECHE OS OLHOS

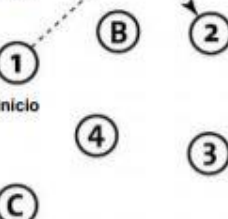
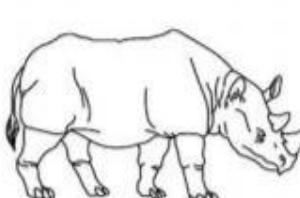
MONTREAL COGNITIVE ASSESSMENT (MOCA)

VERSÃO PORTUGUESA – 7.1 VERSÃO ORIGINAL

Nome: _____ Idade: _____

Gênero: _____ Data de Nascimento: _____

Escolaridade: _____ Data de Avaliação: _____

VISUO-ESPACIAL / EXECUTIVA						Pontos		
		Copiar o cubo	Desenhar um Relógio (onze e dez) (3 pontos)		_____/5			
<div style="display: flex; justify-content: space-between;"> [] [] [] [] </div>								
<div style="display: flex; justify-content: space-between;"> Contorno Números Ponteiros </div>								
NOMEAÇÃO								
			<div style="display: flex; justify-content: space-between;"> [] [] [] </div>					
<div style="display: flex; justify-content: space-between;"> [] [] [] </div>								
MEMÓRIA								
Leia a lista de palavras. O sujeito deve repeti-la. Realize dois ensaios. Solicite a evocação da lista 5 minutos mais tarde.	1º ensaio	2º ensaio	Boca	Linho	Igreja	Cravo	Azul	Sem Pontuação
<div style="display: flex; justify-content: space-between;"> [] [] [] [] [] [] </div>								
ATENÇÃO								
Leia a sequência de números. (1 número/segundo)	O sujeito deve repetir a sequência. [] 2 1 8 5 4 O sujeito deve repetir a sequência na ordem inversa. [] 7 4 2					_____/2		
Leia a série de letras (1 letra/segundo). O sujeito deve bater com a mão cada vez que for dita a letra A. Não se atribuem pontos se ≥ 2 erros.								
[] FBACMNAAJKLBAFAKDEAAAJAMOFAB								
Subtrair de 7 em 7 começando em 100.	[] 93	[] 86	[] 79	[] 72	[] 65	_____/3		
4 ou 5 subtrações correctas: 3 pontos; 2 ou 3 correctas: 2 pontos; 1 correcta: 1 ponto; 0 correctas: 0 pontos								
LINGUAGEM								
Repetir: Eu só sei que hoje devemos ajudar o João.	[] O gato esconde-se sempre que os cães entram na sala.					_____/2		
Fluência verbal: Dizer o maior número possível de palavras que comecem pela letra "P" (1 minuto).								
[] _____ (N ≥ 11 palavras)								
_____/1								
ABSTRACÇÃO								
Semelhança p.ex. entre banana e laranja = fruta [] comboio • bicicleta [] relógio • régua								
_____/2								
EVOCAÇÃO DIFERIDA								
Deve recordar as palavras SEM PISTAS	Boca	Linho	Igreja	Cravo	Azul	Pontuação apenas para evocação SEM PISTAS		
<div style="display: flex; justify-content: space-between;"> [] [] [] [] [] </div>								
Opcional	Pista de categoria							
Pista de escolha múltipla								
_____/5								
ORIENTAÇÃO								
[] Dia do mês	[] Mês	[] Ano	[] Dia da semana	[] Lugar	[] Localidade	_____/6		
© Z.Nosreddine MD								
Examinador: _____								
TOTAL _____/30								

Age	Educational Level (years)				
	Primary (1-4)	Middle (5-9)	High (10-12)	University (>12)	All education
(n)	(29)	(66)	(59)	(60)	(214)
25-49	23.55 ± 2.56	26.42 ± 2.18	27.39 ± 1.86	28.83 ± 1.38	26.98 ± 2.55
*SD	21 - 20 - 18	24 - 23 - 22	26 - 25 - 24	28 - 27 - 26	24 - 23 - 22
(n)	(91)	(59)	(33)	(35)	(218)
50-64	21.78 ± 2.86	25.58 ± 2.25	26.61 ± 2.28	27.51 ± 2.13	24.46 ± 3.43
*SD	19 - 18 - 16	23 - 22 - 21	24 - 23 - 22	25 - 24 - 23	21 - 19 - 18
(n)	(136)	(45)	(20)	(17)	(218)
≥ 65	21.27 ± 3.37	24.60 ± 2.87	25.11 ± 1.94	26.35 ± 1.87	22.71 ± 3.60
*SD	18 - 16 - 15	22 - 20 - 19	23 - 22 - 21	25 - 24 - 23	19 - 17 - 16
(n)	(256)	(170)	(112)	(112)	(650)
All age	21.71 ± 3.18	25.65 ± 2.50	26.77 ± 2.15	28.04 ± 1.94	24.70 ± 3.67
	19 - 17 - 15	23 - 22 - 21	25 - 24 - 23	26 - 25 - 24	21 - 19 - 17

* MoCA values below 1S.D., 1.5S.D and 2S.D., respectively.

Normative data of the MoCA scores according to age and educational level (Freitas S, Simões MR, Alves L, Santana I. Montreal Cognitive Assessment (MoCA): normative study for the Portuguese population. J Clin Exp Neuropsychol. 2011 Nov;33(9):989-96. doi: 10.1080/13803395.2011.589374.)

Action research arm test

Nos sub-testes garra e pinçamento, o paciente sentado em frente a uma mesa deve pegar e manter objectos (por exemplo, cubos de tamanhos diferentes) e colocá-los em uma prateleira de 37,5 cm de altura colocada sobre a mesa.

Na escala ARAT, uma pontuação de “zero” representa incapacidade para realizar qualquer parte da tarefa e “um” (1) quando o paciente realiza partes da tarefa. A pontuação “dois” (2) na escala ARAT deve ser atribuída se o paciente realiza completamente a tarefa, mas com tempo excessivo, dificuldade ou ainda com padrões anormais de movimento ou movimentos compensatórios de tronco, e, finalmente, o score “três” (3) será assinalado quando a tarefa for realizada perfeitamente

(3, realiza o teste normalmente; 2, completa o teste, mas leva mais tempo que o normal ou tem grande dificuldade; 1, realiza o teste parcialmente; 0, não consegue executar qualquer parte do teste)

Há quatro subtestes: compressão, preensão, pinçar e movimento grosso.

Os itens estão ordenados de modo que:

- se o sujeito passar no primeiro item, os restantes não precisam de ser administrados e atribui-se o máximo para esse subteste;
- se o sujeito falha o primeiro e falha o segundo, é-lhe atribuído zero, e, novamente, não precisam ser executados mais testes nesse subteste;
- se nada disto ocorrer, ele precisa completar todas as tarefas dentro do subteste

Tarefa	Cotação
Grasp / compressão (agarrar firmemente)	
1. Bloco de 10 cm de madeira (se conseguir cotar = 3, total = 18 e passar para preensão) (4,2'')	
Pegue um bloco de 10 cm	
2. Bloco de 2.5 cm de madeira (se cotação = 0, total = 0 passa a preensão)	
Pegue um bloco de 2.5 cm (3,6'')	
3. Bloco de 5 cm de madeira (3,5'')	
4. Bloco de 7.5 cm de madeira (3,9'')	
5. Bola de (Cricket), com 7.5 cm diâmetro (3,8'')	
6. Pedra 10 x 2.5 x 1 cm	
Grip / preensão (pegar)	
7. Passar a água de um copo ao outro (se cotado = 3, total = 12, passa a pinça) (7,9'')	
8. Tubo 2.25 cm (If score = 0, total = 0, passa a pinçamento) (4,2'')	
9. Tubo 1 x 16 cm (4,3'')	
10. Colocar anilha num parafuso (3.5 cm diâmetro) (4'')	
Pinch / pinça (apertar)	
11. Rolamento, 6 mm, entre o terceiro dedo e o polegar (se score = 3, total = 18 ir Grossmt) (4,4'')	
12. Berlinde, 1.5 cm, entre o primeiro dedo e o polegar (se score = 0, total = 0 ir Grossmt) (4,1'')	
13. Rolamento entre o segundo dedo e o polegar (4,1'')	
14. Rolamento entre o primeiro dedo e o polegar (4'')	
15. Colocar o berlinde entre o terceiro dedo e o polegar (3,8'')	
16. Colocar o berlinde entre o segundo dedo e o polegar (3,8'')	
Gross Movement/ Movimento grosso	
17. Colocar a mão atrás da cabeça (If score = 3, total = 9 e terminar ou se score = 0, total = 0 terminar) (2,7'')	
18. Colocar a mão no topo da cabeça (2,7'')	
19. Levar a mão à boca (2,4'')	
Total	

Borges, G. (2007). Teste da Ação da Extremidade Superior como medida de comprometimento após, 277-283.

Van der Lee, J. H., De Groot, V., Beckerman, H., Wagenaar, R. C., Lankhorst, G. J., & Bouter, L. M. (2001). The intra- and interrater reliability of the action research arm test: a practical test of upper extremity function in patients with stroke. *Arch Phys Med Rehabil*, 82(1), 14-9. doi: 10.1053/apmr.2001.18668.

Yozbatiran, N., Der-Yeghian, L., & Cramer, S.C. (2008). A standardized approach to performing the action research arm test. [Validation Studies]. *Neurorehabil and Neural Repair*, 22(1), 78-90. doi: 10.1177/1545968307305353

Motor assessment scale - Membro superior

Instruções: Percorrer os itens por ordem de dificuldade. Pontuação '1' se o paciente consegue realizar a actividade, '0' se não pode. Três tentativas são permitidas para cada item. Você pode parar a secção membro superior se após três tentativas consecutivas obtiver '0' para três itens consecutivos. Todos os testes do membro superior referem-se ao lado afectado salvo indicação em contrário.

Tarefa

Item 6: Função do membro superior

1. Deitado, protraí o ombro com membro superior em elevação. (Avaliador posiciona o membro superior na posição e o suporta com cotovelo em extensão). _____
2. Deitado, mantém o membro superior estendido em elevação por 2 segundos. (Cotovelo em até 20 graus de extensão completa. O avaliador pode posicionar o Membro superior na posição, e o paciente deve manter com certa rotação externa). _____
3. O paciente realiza flexão e extensão do cotovelo para levar a palma da mão à testa com o Membro superior posicionado como no score 2. (O avaliador pode auxiliar na supinação do antebraço). _____
4. Sentado, mantém o membro superior estendido em flexão de 90 graus em relação ao corpo por 2 segundos. (O avaliador pode colocar o membro superior na posição, e o paciente deve manter com alguma rotação externa e extensão de cotovelo. Não permitir elevação excessiva do ombro). _____
5. Sentado, paciente levanta o membro superior como acima, mantém por 10 segundos e depois abaixa-o. (Paciente deve manter a posição com certa rotação externa. Não permitir a pronação). _____
6. Em ortostasia, mão contra a parede. Manter a posição do Membro superior enquanto gira o corpo em direção à parede. (Membro superior abduzido a 90 graus, palma da mão contra a parede). _____

Item 7: Movimento das mãos

1. Sentado, extensão do punho. (O avaliador posiciona o paciente sentado com apoio do antebraço na mesa. O avaliador coloca um objecto cilíndrico na palma da mão do paciente. O paciente é instruído a levantá-lo da mesa, realizando extensão do punho. Não permitir flexão do cotovelo). _____
2. Sentado, desvio radial do punho. (O avaliador pode posicionar o antebraço em posição neutra, isto é, apoio sobre o lado ulnar, polegar alinhado ao antebraço e o punho em extensão, dedos ao redor de um objecto cilíndrico. Paciente é instruído a elevar a mão da mesa. Não permitir a flexão ou pronação do cotovelo). _____
3. Sentado, cotovelo lateralmente, efectua pronação e supinação. (Cotovelo sem suporte e em ângulo recto. $\frac{3}{4}$ do movimento é aceitável). _____
4. Alcançar à frente, pegar numa bola de 14 centímetros de diâmetro com ambas as mãos e colocar no colo. (Bola deve estar em uma mesa distante e à frente do paciente, de modo que ele estenda os seus membros superiores totalmente para alcançá-la. Ombros devem estar protraídos, cotovelos estendidos, punhos neutros ou estendidos. Palmas das mãos devem estar em conta com a bola). _____
5. Pegar um copo de plástico da mesa e colocá-lo na mesa cruzando o outro lado do corpo. (Não permitir alteração na forma do copo). _____
6. Oposição contínua do polegar em cada dedo, mais de 14 vezes em 10 segundos. (Cada dedo deve tocar o polegar, iniciando pelo dedo indicador. Não permitir que o polegar desvie na direção dos dedos nem vá para trás). _____

Item 8: Actividades avançadas da mão

1. Pegar numa tampa de uma caneta e colocá-la para baixo novamente. (Paciente estica o membro superior para frente, pega a tampa da caneta, solta na mesa próximo ao corpo). _____
2. Retirar feijões de uma chávena e colocar noutra. (A chávena de chá contém 8 feijões. Ambas as chávenas devem estar na distância do comprimento do membro superior. Mão direita pega no feijão da chávena à esquerda e coloca na chávena à direita). _____
3. Desenhar linhas horizontais que param numa linha vertical, dez vezes em 20 segundos. (Pelo menos cinco linhas devem tocar e parar na linha vertical). _____
4. Segurar um lápis fazendo pontos rápidos e consecutivos numa folha de papel. (Paciente deve realizar ao menos dois pontos por segundo, durante 5 segundos (ponto, e não risco). O paciente pega e posiciona o lápis sem auxílio. Paciente deve segurar o lápis como se fosse escrever. Paciente deve fazer ponto, e não traço). _____
5. Levar uma colher de sobremesa com líquido até a boca. (Não permitir que a cabeça se abaixe até a colher. Não permitir que o líquido derrame). _____
6. Segurar um pente e pentear o cabelo na região posterior da cabeça. _____

Total

Carvalho, T. B., Relvas, P. C. A., Neves, R. C. M., & Rosa, S. F. (2009). Confiabilidade, compreensão e aceitação da versão em português da Motor Assessment Scale em pacientes com acidente vascular. *Rev Bras Fisioter*; 13(5), 405-411.

Sabari, J. S., Lim, A. L., Velozo, C. a, Lehman, L., Kieran, O., & Lai, J.-S. (2005). Assessing arm and hand function after stroke: a validity test of the hierarchical scoring system used in the motor assessment scale for stroke. *Arch Phys Med Rehabil*, 86(8), 1609-15. doi: 10.1016/j.apmr.2004.12.028.

Fugl-Meyer assessment scale – arm section

Tarefa	Pontuação
III. Função motora de membro superior	
1 – Motricidade reflexa: Bíceps , flexores dos dedos, Tríceps ()	0 – sem actividade reflexa 2 – actividade reflexa presente
2 – Sinergia flexora: Elevação (), retração de ombro (), abdução + 90 (), rot. Externa (), flexão de cotovelo (), supinação () Pont. máx:(12) 3 – Sinergia extensora: adução do ombro (), rot. Interna (), extensão cotovelo (), pronação () Pont. máx:(8)	0 – tarefa não pode ser realizada completamente * 1 – tarefa pode ser realizada parcialmente 2 – tarefa é realizada perfeitamente
4 – Movimentos com e sem sinergia: a) mão até à coluna lombar () b) flexão de ombro 0° até 90° () c) prono-supinação (cotov. 90° e ombro 0°) () d) abdução ombro 0° a 90° com cotov. estendido e pronado () e) flexão de ombro de 90° a 180° () f) prono-supinação (cotov. 0° e ombro fletido de 30 a 90° () Pont. máx: (12)	a) * b) 0 – se o início do mov. o braço é abduzido ou o cotovelo é fletido 1 – se na fase final do mov., o ombro abduz e/ou ocorre flexão de cotovelo 2 – a tarefa é realizada perfeitamente c) 0 – Não ocorre posicionamento correto do cotovelo e ombro e/ou pronação e supinação não pode ser realizada completamente 1 – prono-supino pode ser realizada com ADM limitada e ao mesmo tempo o ombro e o cotovelo estejam corretamente posicionados 2 – a tarefa é realizada completamente d) 0 – não é tolerado nenhuma flexão de ombro ou desvio da pronação do antebraço no INÍCIO do movimento 1 – realiza parcialmente ou ocorre flexão do cotovelo e o antebraço não se mantém pronado na fase TARDIA do movimento 2 – a tarefa pode ser realizada sem desvio e) 0 – o braço é abduzido e cotovelo fletido no início do movimento 1 – o ombro abduz e/ou ocorre flexão de cotovelo na fase final do movimento 2 – a tarefa é realizada perfeitamente f) 0 – Posição não pode ser obtida pelo paciente e/ou prono-supinação não pode ser realizada perfeitamente 1 – actividade de prono-supinação pode ser realizada mesmo com ADM limitada e ao mesmo tempo o ombro e o cotovelo estejam corretamente posicionados 2 – a tarefa é realizada perfeitamente
5 – Actividade reflexa normal: () bíceps / tríceps/ flexor dedos (avalía-se o reflexo <u>somente se o paciente atingiu nota 2 para os itens d), e), f)</u> do item anterior) Pont. máx:(2)	0 – 2 ou 3 reflexos estão hiperactivos 1 – 1 reflexo esta marcadamente hiperactivo ou 2 estão vivos 2 – não mais que 1 reflexo está vivo e nenhum está hiperactivo
6 – Controlo de punho: a) Cotovelo 90°, ombro 0° e pronação, c/ resistência. (assistência, se necessário) () b) Máxima flexão-extensão de punho, cotov. 90°, ombro 0°, dedos fletidos e pronação (auxílio se necessário) () c) Dorsiflexão com cotovelo a 0°, ombro a 30° e pronação, com resistência (auxílio) () d) Máxima flexão-extensão, com cotov. 0°, ombro a 30° e pronação (auxílio) () e) Circundução () Pont. máx:(10)	a) 0 – o paciente não pode dorsiflectir o punho na posição requerida 1 – a dorsiflexão pode ser realizada, mas sem resistência alguma 2 – a posição pode ser mantida contra alguma resistência b) 0 – não ocorre mov. voluntário 1 – o paciente não move ativamente o punho em todo grau de movimento 2 – a tarefa pode ser realizada c) Idem ao a) d) Idem ao b) e) Idem ao b)
7–Mão: a) flexão em massa dos dedos () b) extensão em massa dos dedos () c) Preensão 1: Art. metacarpofalangeanas (II a V) estendidas	a) * b) 0 - nenhuma actividade ocorre 1 – ocorre relaxamento (liberação) da flexão em massa 2 – extensão completa (comparado com mão não afetada)

<p>e interfalangeanas distal e proximal fletidas. Preensão contra resistência ()</p> <p>d) Preensão 2: O paciente é instruído a aduzir o polegar e segurar um papel interposto entre o polegar e o dedo indicador ()</p> <p>e) Preensão 3: O paciente opõe a digital do polegar contra a do dedo indicador, com um lápis interposto ()</p> <p>f) Preensão 4: Segurar com firmeza um objecto cilíndrico, com a superfície volar do primeiro e segundo dedos contra os demais ()</p> <p>g) Preensão 5: o paciente segura com firmeza uma bola de ténis ()</p> <p>Pont. máx: (14)</p>	<p>c) 0 – posição requerida não pode ser realizada 1 – a preensão é fraca 2 – a preensão pode ser mantida contra considerável resistência</p> <p>d) 0 – a função não pode ser realizada 1 – o papel pode ser mantido no lugar, mas não contra um leve puxão 2 – um pedaço de papel é segurado firmemente contra um puxão</p> <p>e) 0 – a função não pode ser realizada 1 – o lápis pode ser mantido no lugar, mas não contra um leve puxão 2 – o lápis é segurado firmemente</p> <p>f) 0 – a função não pode ser realizada 1 – o objecto interposto pode ser mantido no lugar, mas não contra um leve puxão 2 – o objecto é segurado firmemente contra um puxão</p> <p>g) 0 – a função não pode ser realizada 1 – o objecto pode ser mantido no lugar, mas não contra um leve puxão 2 – o objecto é segurado firmemente contra um puxão</p>
<p>IV. Coordenação/ Velocidade MS:</p> <p>a) Tremor ()</p> <p>b) Dismetria ()</p> <p>c) Velocidade: Indicador-nariz 5 vezes, e o mais rápido que conseguir ()</p> <p>Pont. máx: (6)</p>	<p>a) 0 – tremor marcante/ 1 –tremor leve/ 2 –sem tremor</p> <p>b) 0 – dismetria marcante/ 1 – dismetria leve/ 2 –sem dismetria</p> <p>c) 0 – 6 seg. mais lento que o lado não afectado/ 1 – 2 a 5 seg. mais lento que o lado não afectado/ 2 – menos de 2 segundos de diferença</p>
Total	

Sanford, J., Moreland, J., Swanson, L. R., Stratford, P. W., & Gowland, C. (1993). Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. *Physical therapy*, 73(7), 447-54

T, M. A. K. I., Emab, Q. U., Ewa, C. A., Lps, P. A. Z., Nh, N. A., Mmea, I. N., et al. (2006). ESTUDO DE CONFIABILIDADE DA APLICAÇÃO DA ESCALA DE FUGL-MEYER NO BRASIL. *Rev. bras. fisioter.*, 10(2), 177-183.

4. Nome do Observador e nº da ordem

Muito obrigado!

Raquel Carvalho