BCI THERAPIES TRIGGERING SENSORY FEEDBACK FOR MOTOR REHABILITATION AFTER STROKE: A SYSTEMATIC REVIEW

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ABSTRACT: In the last two decades, brain-computer interfaces (BCI) triggering external devices to perform movements for upper-limb rehabilitation after stroke, have proven to be successful. However, the literature is quite heterogeneous in terms of targeted patient population and study protocols. In this systematic review, we aim at identifying those patient characteristics and protocol features that might best explain the variance observed in treatment-induced motor recovery. Using the data from 15 studies and a total of 168 patients with a BCI-based intervention, patients in the sub-acute phase and mildly impaired patients showed significantly stronger improvement with the BCI-based intervention. Furthermore, receiving conventional therapy additionally to the BCI-based intervention leads to a significantly larger improvement. In summary, BCI-based neurorehabilitation combined with conventional therapy might induce a synergistic effect leading to stronger functional recovery. Larger patient samples in studies and more information on individuals characteristics and protocol features would be desirable in order to build predictive models for motor rehabilitation towards personalization of interventions.

INTRODUCTION

In the last two decades, the use of rehabilitation technologies for motor recovery after stroke has increased [1]. Among these, BCI is a very promising technology. Its goal is to re-create contingency between voluntary brain activation in the motor cortex, movement induction and afferent peripheral sensory feedback, often given by an exoskeleton or functional electrical stimulation (FES). This contingent activation of the efferent (motor) and afferent (sensory) part of movements is thought to be one of the main neurophysiological mechanisms BCI-based therapy relies on. This leads to neuroplastic changes following Hebbian learning principles supporting reorganization and the recovery process. This intended contingency is achieved with the following framework: brain activity is continuously recorded and fed to a decoding algorithm trained to differentiate between specific brain states (e.g. rest vs. motor intention); whenever such signal is detected, an external device/machine is triggered to perform a motor action and provide a well-timed sensory feedback contingent to brain engagement. BCI is still a relatively new technology for stroke rehabilitation and the current literature is mainly based on proof-of-principle clinical trials targeted to provide first evidence for feasibility and efficacy of this intervention in comparison to more standard rehabilitation treatments. Meta-analyses on the topic [2,3] have shown that BCI therapies result in significantly stronger motor improvement compared to various controls (i.e. standard therapy [4,5], external device alone [4,6,7], sham BCI where feedback is given randomly, but with the same external device [8,9,10]). Certainly, these reviews and the respective trials highlight the potential of BCI-based rehabilitation for motor recovery after stroke. Although a positive effect of BCI-based rehabilitation has been suggested, the BCI protocols used are not standardized and are quite heterogeneous; the same applies to the targeted patient population in the different trials. Therefore, the present review addresses whether specific intervention parameters relate better to stronger motor recovery in experiments using BCI-based therapy.

Considering all the studies (controlled and non-controlled) that recruited stroke patients for motor rehabilitation using BCIs, large differences in outcome measures, protocol design, as well as individual patient characteristics are apparent. Main differences are found e.g., in total intervention duration, external device used, performed movements, and in terms of individual patient characteristics, impairment at baseline and stroke onset. The goal of our systematic review is to determine, within BCI studies, how the degree of motor recovery is related to these features.

MATERIALS AND METHODS

Articles retrieval strategy and inclusion criteria: Within this review, protocols and patient characteristics which could be potential parameters for predicting motor recovery in stroke patients were evaluated. The retrieval of relevant papers used the following keywords in Google Scholar research: brain-computer/machine/robotic interface, exoskeleton/orthosis/robot, functional/neuromuscular electrical stimulation, upper-limb, stroke, rehabilitation. In addition, we looked through the references of the retrieved papers and reviews on the topic. Papers

Table 1 –Characteristics of selected studies

Reference	Sample	Age(y)	Stoke onset (months)	Motor impairment (baseline)	Brain instruction	Sensory feedback provider	Standard therapy (hours)	BCI therapy (hours)	Additional feedbacks	Outcomes	Movement[1]
Biasiucci et al., 2018 [9]	14	56.35±9.55	56.35±9.55	Moderate-to-severe	AM	FES	7.5	10	Therapist	FMA	Hand extension
Ramos-Murguialday et al., 2013 [8]	16	49.3 ± 12.5	49.3 ± 12.5	Severe	AM	EXO	20	20	None	FMA	Reach and grasp
Pichiorri et al., 2015 [15]	14	64.1 ± 8.4	64.1 ± 8.4	Moderate-to-severe	MI	EXO	36	12	Therapist	FMA	Fingers extension
Li et al., 2014 [7]	7	66.3±4.53	66.3±4.53	Severe	MI	FES	40	24	Visual and auditory	FMA, ARAT	Hand extension
Sullivan et al., 2015 [18]	6	57.5±7.25	51.5±38.27	Mild	AM	FES	0	7.5	None	FMA	Elbow flexion
Bundy et al., 2017 [19]	10	58.6±9.72	73.6±98.86	Moderate-to-severe	MI	EXO	0	40.2	Visual	ARAT	3-finger pinch
Várkuti et al., 2013 [20]	6	40.17±13.23	15.78±12.33	Mild-to-moderate	MI	EXO	0	24	None	FMA	Shoulder elbow flexion
Frolov et al., 2017 [10]	55	58.0 [48.0; 65.0]	8.0 [4.0; 13.0]	Mild-to-severe	MI	EXO	0	5	Visual	FMA, ARAT	Hand extension
Tabering et al., 2018 [14]	8	61.25±18..96	36.75±24.18	Severe	MI	FES	0	60	None	FMA	Hand extension
Prasad et al., 2017 [16]	4	-	chronic	Mild-to-severe	MI	EXO	0	12	Visual	ARAT	Hand extension
Caria et al., 2011 [21]	1	67	14	Severe	MI	EXO	40	40	Visual	FMA	Fingers flexion
Mukaino et al., 2015 [22]	1	38	14	Moderate	AM	FES	6.6	8.3	None	FMA	Fingers extension
Belardinelli et al., 2017 [23]	8	57.25±11.02	75.5±36.78	Severe	MI	FES	0	7	None	FMA	Fingers extension
Remisk et al., 2018 [11]	14[2]	60.43±13.4	42.64±50.06	No restriction	AM	FES	0	30	Visual	ARAT	Fingers extension
Ibáñez et al., 2017 [17]	4	54.25±11.84	48±9.78	Mild	AM	FES	0	8	None	FMA	Reach and grasp

[1] If extension or flexion, it means also movement in the other direction

[2] The actual sample number was 19, however 5 patients were recruited with already the maximal score (57 in the ARAT) and remained stable. Therefore, they were not included since they did not have any window for recovery

published until the end of 2018 were considered. Moreover, only studies that reported clinical motor assessment were included. In particular, for this preliminary review, we only accepted studies using the Fugl-Meyer Assessment (FMA) or the Action Research Arm Test (ARAT) since they are the most widely used scales and because a correlation between the two has already been extensively confirmed [11,12]. Given the objective of this review, we could only include articles reporting the motor improvement for each patient (i.e. if only the average recovery of a group was given, the study was not considered). If the study was a randomized trial, we only considered patients in the experimental therapy. Finally, due to this "individuality" feature we had no limitation in sample size. Whenever an eligible article was lacking data, we tried to contact the authors multiple times.

Analyses methods: In terms of study protocol, we looked at six characteristics. (1) The device giving the sensory feedback and (2) the type of movement produced. (3) The type of instruction to calibrate and exploit the BCI was also considered, specifically we divided into motor imagery (with no inner subdivision, as most studies explicitly say they used the kinesthetic type) and active motor intention ("try to move the arm/hand"). (4) The additional feedbacks received (e.g. visual, auditory, tongue stimulation). (5) Overall intervention therapy and (6) if any, additional standard therapy. When possible, some characteristics of the patients were also taken into account: motor impairment at baseline and the time after stroke in months.

In these analyses the dependent variable is always the motor improvement. For each binary comparison, we computed non-parametric tests for the means, namely the Mann-Whitney test and the effect size with the *Cohen's d* [13]. For non-binary features, such as the intervention duration, we looked at the correlation. Along the article, we will refer to motor improvement as the difference in motor score between the end and the beginning of the study. We will call proportional motor improvement the motor improvement normalized by the baseline. All the values are normalized by the maximal achievable score. This choice was made since some studies used a modified FMA [8,14] and because the maxima of the ARAT and the FMA differ.

RESULTS

Search results: The pruned research gave overall 30 eligible papers. Of these, 6 were redundant reports, 1 used both motor imagery and attempt the movement as instruction, 3 used no motor scale, 2 did not assess motor abilities with FMA nor ARAT and 3 did not report the motor scores for each subject. This left us with 15 papers.

Overall characteristics of protocols and samples: A summary of study protocols and overall subject characteristics for each of the 15 articles can be found in Table 1. In total, we included 168 patients who underwent non-invasive BCI therapy that triggered sensory feedback. For 120 of them, the device used was an exoskeleton. The remaining received above motor-threshold FES. Additional feedbacks ranged in terms of visual response (6 studies), the therapist voice (2 studies) or tongue stimulation (1 study). In some cases, more than one additional feedback was given. Overall intervention time ranged between 5 and 64 hours (μ=17.13 σ=16.76). Some studies also involved conventional therapy (if present, it was between 7.50 and 40 hours, sometimes in higher amount compared to the experimental therapy [7,15]). In terms of personal characteristics, we could not retrieve the age and sex for most of the time. However, 83 subjects (chronic patients) had a stroke more than 6 months before participating in the experiment (μ=53.88, σ=53.03 months) and 26 were sub-acute (μ=2.83, σ=1.06 months). For two studies [10,16] this parameter was not given. In terms of severity of impairment, almost half of the subjects were severe (FMA<=20 and ARAT<=20) and the remaining moderate-to-mild (here we refer to mild as less impaired than moderate).

Patient characteristics: For patient individual characteristics only stroke onset and impairment at baseline was investigated, due to lack of data for other parameters (e.g. age, lesion side). In Fig. 1 the difference between binarized groups of subject is displayed: chronic vs. acute/sub-acute, severe vs. moderate/mild and the combination of the former. Patients in the sub-acute phase showed significantly better recovery compared to the other groups (Fig. 1b), the same can be observed for patients who are rather mildly impaired before starting the experiment (Fig. 1a). When combining the two groups (chronic and severe vs. sub-acute and moderately impaired), the effect size is increasing.

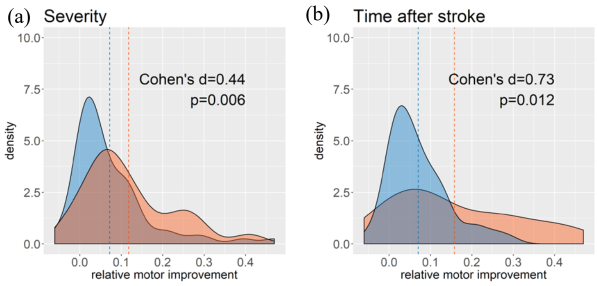

Figure 1 – Density plots for comparison between patients' characteristics and their motor improvement, normalized by the maximum score. We consider their impairment at baseline (severe or not) and the chronicity (stroke occurred more than 6 months before study). **(a)** Impairment at baseline; **(b)** chronicity. In blue: severe and chronic, in red: moderate–to-mild impairment and sub-acute patients respectively. The dashed lines represent the mean of each contribution.

Protocol features: One source of variance for the motor improvement comes from the subjects' characteristics, another from the design of the experimental protocol. The 15 studies considered all differed in terms of intervention time, duration (if any) of an additional conventional therapy, type of instruction to command the BCI and the device exploited for sensory feedback. The type of movement triggered by the BCI also changed among studies. We divided them into proximal (shoulder, arm and elbow), distal (hand and wrist) and movements combining distal and proximal parts (e.g. reach and grasp). As motor improvement also significantly differed according to the baseline, we decided to use proportional improvement of motor functions as dependent variable to take into account baseline differences and give stronger importance to improvements in severe patients. We acknowledge that there are also other computational approaches that could have been used [15]. Due to space limitations detailed technical aspects related to BCI and EEG recordings were not addressed in the review; also, thorough information about these aspects is often not available. Nevertheless, it is obvious that the processing pipelines used, as well as the classifiers, were quite heterogeneous. The targeted brain signal was mainly the sensorimotor rhythm, but recorded from different areas; moreover, the pre-processing pipeline varied and the decoding algorithm ranged from support vector machine to common-spatial patterns, from naïve Bayes and Gaussian classifiers to independent component analysis.

Firstly, instructions given to subjects to command the BCI were addressed. In most papers, they were asked to perform motor imagery (MI) and in fewer to try and make the movement that the device would have then actually completed. Patients using MI, had a better recovery compared to the other group with a moderate, but not significant effect size (d=0.3). Attempting the movement was never tried in studies that included non-severe subjects to avoid the possibility of some actively initiated movements for only a subgroup. However, the results did not change when we only looked at severe patients. This may be due to the fact that proportional improvement rather than motor improvement was used.

No significant difference in recovery was observed when comparing the devices used, nor the number of additional feedback provided.

Interesting results can be observed when looking at the proportional improvement according to the movement performed. All the movements were quite simple (e.g., hand opening, elbow flexion) and only in two study more complex ones (i.e. reaching and grasp [8,17]) were attempted. For these specific cases, complexity goes along with an action involving distal and proximal parts. Fig. 2 shows significant larger improvement when the latter types are performed compared to movements involving either part.

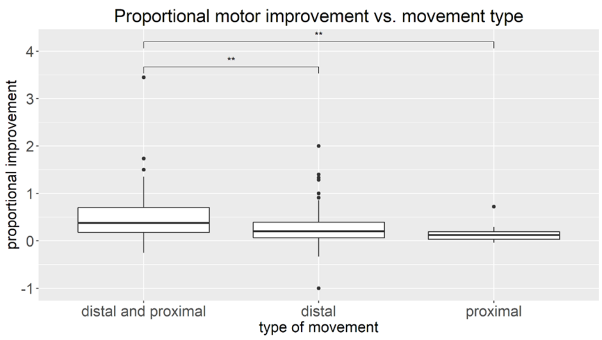

Figure 2 – Proportional motor improvement according to type of movement trained with either device. There is a significant difference in recovery when a movement involving both distal and proximal parts of the upper-limb is used compared to movements involving only one part. ** p<=0.001

Other significant results arose when studying the explicit use of conventional therapy in parallel with the experimental one. Initially, we grouped the subjects according to whether or not they received additional standard therapy. The effect size was quite strong (d=0.5), and the two distributions significantly different (p<0.001) with the group receiving conventional therapy showing larger improvement. Secondly, we stratified patients into more groups according the total amount of standard therapy received and reported the results in Fig. 3a. Examining correlations between the total amount of therapy received and the respective proportional improvement, we found r=0.34, p<0.001. However, no significant correlation was found when looking at the total amount of experimental therapy. Finally, we summed the total hours of therapy (experimental with BCI and standard) and found a strong correlation (r=0.24, p<0.01). Boxplots can be seen in Fig. 3b.

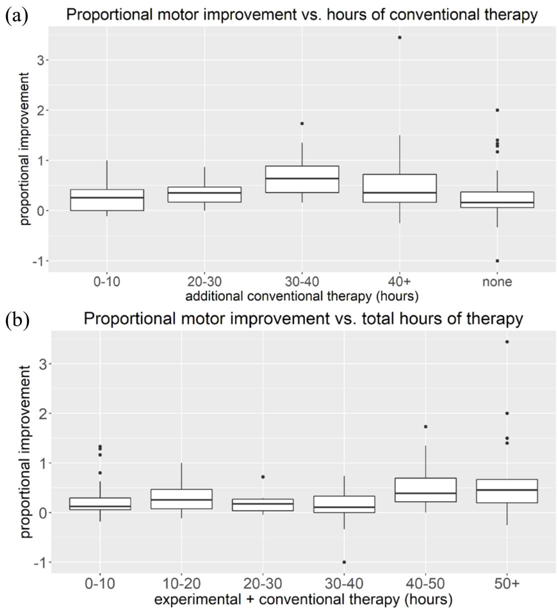

Figure 3 – Proportional motor improvement compared to overall hours of therapy received. **(a)** Additional conventional therapy; **(b)** sum of interventional and conventional therapy. If not explicitly specified in the study protocol, standard therapy was considered as none.

DISCUSSION

This systematic review aimed at looking at possible relationships between patient and study protocol characteristics and motor improvement of the upper-limb. The target population was stroke patients who managed to control a BCI to trigger an external device for supporting the movement and delivering sensory feedback; specifically, we looked at studies with FES or exoskeletons.

Stroke onset and severity at baseline: chronicity and severity of impairment at baseline were found to be both important features. As expected, the group of sub-acute patients generally improved more compared to the chronic ones. This is probably due to the "high-neuroplasticity window" that opens for around 8-12 weeks right after the stroke incident in which also the brain naturally starts to re-organize [24]. During this period re-learning processes are more efficient and efficacious [25]. Overall, this result is in agreement with recent meta-analyses on BCI rehabilitation [2]. We also observed that starting at a lower level of motor capability leads to smaller improvement, even though the range for improvement is much higher. Considering that often larger impairment results from larger lesions, it seems reasonable that the capability for reorganization, plastic changes and re-learning might be limited.

Motor imagery vs. attempted movement: Among the protocol design features, we were expecting to see larger improvement when the instruction to command the BCI was to try to attempt the movement rather than MI, as this should try to re-activate the "normal" motor pathways. Yet, there is a great overlap between MI and real-movement pathways. This correspondence has been proven both with fMRI studies [26] and in terms of physics law preservation in MI, such as the Fitt's law of timing [27]. In this analysis, it seems that MI leads to a larger, although not statistically significant, recovery. A clear limitation here is that the number of patients for the two groups is very different, being the group of MI almost double in size compared to the other. Furthermore, the group attempting to do the movement is composed only of severe patients, who generally have lower performance. Nonetheless, when focusing only on hemiparetic stroke subjects, the results do not differ much. Therefore, a feature to look at, rather than the instruction given, is the BCI classifier and the accuracy obtained. However, because the primary outcome of all the included studies was motor recovery, the classifier algorithm exploited was seldom reported in detail. Moreover, it was seen that performance, whenever reported, had been computed in different manners (i.e. different proportions between true/false positive/negatives), making comparisons difficult.

Movement type: We found significantly stronger motor recovery when the repeated movement contained joints in both the proximal and the distal part of the upper-limb. Moreover, there was a slight trend for which distal movements perform better than proximal ones, though the difference is not statistically significant. Overall, findings from this section suggest that doing more complex movements, and possibly different types of movement during the BCI therapy, may lead to better motor improvement [28]; additive effects may be obtained with functional movements [5]. At this regard, we speculate that more movements can be achieved by combining an orthosis with FES. Such a union has already been tested in other studies, but rarely triggered by a BCI [29].

Therapy quality or quantity?: In one out of three reviewed studies, for a total of 53 patients, conventional therapy was provided in addition to the experimental one. From the current analyses, patients who received it showed significantly better improvement, with a strong effect size. Furthermore, the amount of training hours significantly correlated with the degree of recovery. A similar correlation was observed when looking at the total amount of therapy, of either type, during the study period. On the contrary, no correlation was found between the total hours of the intervention and motor recovery. It must be pointed out that except for [19], the hours of intervention and additional therapy were kept constant for patients belonging to the same study. Taken together, one could summarize that the addition of standard therapy (1) increases the total amount of therapy and (2) although not working on the synchrony between brain intentions and feedbacks, helps the patient doing more types of movements and especially functional ones. Two randomized clinical trials [4,5] evaluated the difference between BCI and conventional rehabilitation; unfortunately, due to the lack of individual data, they were not included in this review. Nonetheless, in [5] the BCI group received additional therapy, having 50% more overall time of therapy with respect to those receiving only standard. Differently, in [4] the control with standard therapy received an overall same amount of therapy. In both studies, the experimental group improved significantly better than their control and when reported, kept this improvement in the follow-up measurement. To more deeply investigate the role of standard therapy and how a BCI performs compared to it, a randomized clinical trial should be designed in which the total duration for the BCI and the conventional therapy are exactly the same, as well as the performed movements.

Limitations: In this systematic review only studies providing individual data for motor assessment were included. Therefore, the overall sample size was limited. Moreover, the restriction on the motor scales, led to discard some studies. Indeed, adding other motor scales would be relevant. In terms of characteristics, we here only looked at two patients' personal features: motor score at baseline and stroke onset. In further analyses, it would be interesting to add more parameters such as age, lesion site, lesion size or hemispheric dominance and handedness. Due to space limitation technical aspects of BCIs used in rehabilitation settings were also not in detailed scope of this review. To make BCI-based interventions more comparable and standardize them it is of crucial importance that the details about classifiers and analytical pipelines are provided and the different approaches compared. As a brief overview aspects relevant for the classifiers are both the type of pre-processed signal fed to the decoder and the algorithm itself. Furthermore, related to the neurophysiological mechanisms targeted, the location side from which the signal is read is also important and may have an effect on the motor improvement.

Finally, within the present review each feature impacting on the effect of the intervention was addressed separately, however in upcoming meta-analyses it is essential to combine the different aspects and features to develop a strong predictive model.

Recommendations: Limiting factors in these analyses were related to the absence of some features, especially for each individual. A more detailed reporting of individual therapy, BCI-based features, patients' characteristics and treatment durations will also help to better compare studies and develop standards and optimized interventions to maximize the treatment effects. In terms of BCI-therapy, it is important to develop devices which support multiple, functional, longer, and more complex movements. However, at this concern, we acknowledge that multi-class discrimination with non-invasive techniques may be strenuous. Therefore, developments towards hybrid BCI or invasive techniques might pave the way towards these goals.

CONCLUSION

In the present review, we identified five features that show relevance for driving motor recovery of the upper-limb in stroke patients in BCI rehabilitation. In terms of patient characteristics, being in the sub-acute phase and mildly impaired support functional improvement within this treatment strategy. Regarding protocol features, we observed the importance of adding conventional therapy that can be related to both longer rehabilitation duration and more variety and functionality of executed movements.

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