

Clinical EEG and Neuroscience

High intensity chronic stroke motor imagery neurofeedback training at home - three case reports

Journal:	<i>Clinical EEG & Neuroscience</i>
Manuscript ID	EEG-17-0007.R1
Manuscript Type:	Original Manuscript
Keywords:	Motor Imagery, Stroke, Neurorehabilitation, Mobile EEG, Home-based training, neurofeedback
Abstract:	<p>Motor imagery (MI) with neurofeedback has been suggested as promising for motor recovery after stroke. Evidence suggests that regular training facilitates compensatory plasticity, but frequent training is difficult to integrate into everyday life. Using a wireless electroencephalogram (EEG) system, we implemented a frequent and efficient neurofeedback training at the patients' home. Aiming to overcome maladaptive changes in cortical lateralization patterns we presented a visual feedback, representing the degree of contralateral sensorimotor cortical activity and the degree of sensorimotor cortex lateralization. Three stroke patients practiced every other day, over a period of four weeks. Training-related changes were evaluated on behavioural, functional and structural levels. All three patients indicated they enjoyed the training and were highly motivated throughout the entire training regime. EEG activity induced by MI of the affected hand became more lateralized over the course of training in all three patients. The patient with a significant functional change also showed increased white matter integrity as revealed by diffusion tensor imaging, and a substantial clinical improvement of upper limb motor functions. Our study provides evidence that regular, home-based practice of MI neurofeedback has the potential to facilitate cortical reorganization and may also improve associated improvements of upper limb motor function in chronic stroke patients.</p>

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

**High intensity chronic stroke motor imagery
neurofeedback training at home - three case reports**

Short title: Neurofeedback at stroke patients' home

For Peer Review

Abstract

Motor imagery (MI) with neurofeedback has been suggested as promising for motor recovery after stroke. Evidence suggests that regular training facilitates compensatory plasticity, but frequent training is difficult to integrate into everyday life. Using a wireless electroencephalogram (EEG) system, we implemented a frequent and efficient neurofeedback training at the patients' home. Aiming to overcome maladaptive changes in cortical lateralization patterns we presented a visual feedback, representing the degree of contralateral sensorimotor cortical activity and the degree of sensorimotor cortex lateralization. Three stroke patients practiced every other day, over a period of four weeks. Training-related changes were evaluated on behavioural, functional and structural levels. All three patients indicated they enjoyed the training and were highly motivated throughout the entire training regime. EEG activity induced by MI of the affected hand became more lateralized over the course of training in all three patients. The patient with a significant functional change also showed increased white matter integrity as revealed by diffusion tensor imaging, and a substantial clinical improvement of upper limb motor functions. Our study provides evidence that regular, home-based practice of MI neurofeedback has the potential to facilitate cortical reorganization and may also improve associated improvements of upper limb motor function in chronic stroke patients.

Key Words

Motor imagery, Neurofeedback, Stroke, Neurorehabilitation, Mobile EEG, Home-based training

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1. Introduction

Many of the roughly 33 million stroke survivors worldwide per year (1) do not recover completely, so that stroke is one of the leading causes of disability (2). Upper-limb hemiparesis is the most prevalent consequence in stroke survivors (3) with enduring and disabling effects, causing negative impact on quality of life and independence. One approach aiming to facilitate motor recovery after stroke is mental practice with motor imagery (MI). The theoretical foundation of this approach is the neural simulation of action theory (4), which states that executing and imagining the same movement involves similar, overlapping networks. Hence, mental practice with MI may help to prevent non-use driven cortical reorganisation, and facilitate compensatory reorganisation such that in the long run, motor functions improve. Indeed, a number of studies using mental practice with MI as an add-on to physical therapy suggest that MI supports recovery of upper-limb functioning (5–9), resulting in long-lasting behavioural improvements (9).

A more recent development is the combination of MI training with online neurofeedback (NF). This development is closely linked to the notion that feedback in combination with high-intensity task-specific practice is essential for the facilitation of adaptive cortical reorganization (6). Accordingly, NF should help to induce adaptive neural plasticity and thereby contribute to restoring lost motor function (10). Several studies indicate that MI training in combination with NF can indeed induce positive changes at behavioural, functional, and structural levels (11–15). At least one study provides clear evidence that functional changes are more pronounced when MI is combined with NF as compared to MI without NF (16). Moreover, concurrent acquisition of electroencephalogram (EEG) NF and functional magnetic resonance imaging (fMRI) in healthy individuals validated systematic NF effects on cortical

1
2
3 activation patterns (17).
4

5 The effectiveness of neurorehabilitation training regimes such as MI NF is
6 difficult to evaluate, in particular because most approaches are technically
7 demanding, and all of them require frequent, regular practice. The latter issue is of
8 particular importance for stroke victims, because frequent laboratory or hospital visits
9 place a large burden on motor impaired individuals. Without experiencing immediate
10 training effects this effort may negatively impact on a patient's training motivation.
11 Recently developed small and wireless electroencephalogram (EEG) systems may
12 help to overcome this problem. They are portable and low in cost (18,19), perform on
13 par with non-portable EEG systems (20), and soon, NF protocols will be available on
14 smartphone (21).
15
16
17
18
19
20
21
22
23
24
25
26

27 We investigated whether home-based, frequent MI EEG-based NF training is
28 feasible. Specifically, we examined whether chronic stroke patients can stay
29 motivated over a four weeks training period. In addition, we wanted to know whether
30 they experience NF as helpful for MI training. We designed the MI NF protocol to
31 facilitate stronger cortical activity in the ipsilesional than in the contralesional
32 hemisphere in response to MI of the paretic hand. Frequent, high-intensity MI NF
33 should result in systematic behavioural, functional and structural improvements. To
34 assess training effects the home-based training was framed by detailed laboratory-
35 based assessments of motor functions, high-density EEG, structural as well as fMRI,
36 and by diffusion tensor imaging (DTI) of the cortico-spinal tract (CST).
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2. Methods

2.1. Participants

Three individuals with restricted mobility of one upper limb were recruited through a newspaper advertisement (please refer to the Results section for demographic and clinical characteristics). Inclusion criteria were a first-ever, unilateral vascular event, which was at least 6 months ago, and caused permanent motor impairments in the contralesional upper extremity; magnetic resonance imaging (MRI) compatibility; absence of major cognitive deficits as screened with the mini-mental status examination ($MMSE < 25$); and no depressive symptoms as screened with the ‘Geriatric Depression Scale’ ($GDS < 5$). Participants gave written informed consent. The local ethics committee of the University of Oldenburg approved the study.

2.2. Motor imagery neurofeedback training

The training sessions were carried out at the patients’ home, in the presence of an instructor (CS). They comprised a motor imagery (MI) electroencephalogram (EEG)-based neurofeedback (NF) session every other day, including weekends, for a period of four weeks. Cases P20 and P21 completed 14 and case P22 13 training sessions. Fluctuations of time of day when the training was conducted was kept as minimal as possible ($SD < 2.5$ hours). Each session lasted 60 minutes, of which the pre- and post-preparation of the EEG and questionnaires took approximately 25 minutes. The actual MI training lasted approximately 30 min., comprising 3 blocks of roughly 8 min each with 4 min breaks in between. Each of the three blocks was composed of 20 right and 20 left hand trials, which were pseudo-randomly presented using OpenVibe Designer 0.17.1 (22). Participants were instructed to imagine the kinesthetic sensation of a

power grip from the first-person perspective. The MI task interval lasted for 5 s, was cued by a fixation cross 3 s before and was followed by an inter-trial interval of 4.5 to 6 s in steps of 0.5 s (see Fig. 1). During the inter-trial interval participants had the opportunity to initiate a 10 s break via a foot pedal (**Supplemental Methods**).

EEG was recorded from 24 scalp sites using a small, wireless, head-mounted amplifier (mBrainTrain; **Supplemental Methods**). In the first block no NF was given and acquired EEG data were used to derive the necessary parameters for real-time NF delivery in the second block (**Supplementary Methods**). Similarly, data acquired in the second block served as calibration for the NF in the third block. In blocks two and three during the 5 s MI interval real-time NF was provided. The NF protocol developed was based on the observation that chronic stroke is characterized by abnormally strong contralesional sensorimotor activation patterns (23,24). The aim of the training was therefore to restore original cortical lateralization patterns towards a stronger contralateral than ipsilateral activity when MI is conducted with the affected limb. In order to achieve this, the NF signal consisted of a two-dimensional visual display (see Fig. 1). A ball moving along the vertical and horizontal axis indicated the degree of contralateral event-related desynchronization (ERD) and the degree of ERD laterality, the difference between contra- and ipsilateral ERD, respectively (see Fig. 1). The exact position of the ball was determined by the classification of spatially weighted logarithmic band-power features in the range of 8-30 Hz. Additionally, EEG data were analysed offline (**Supplementary Methods**).

--- FIGUR 1 HERE ---

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2.3. Training evaluation

Before and after the four week MI EEG-based NF training upper limb motor performance was assessed using a modified version of the Fugl-Meyer motor assessment (mFMA) (25) and spasticity in the wrist and elbow joints in extension and flexion evaluated using a modified version of the Ashworth scale (MAS)(26). Each test was applied to both the affected and the unaffected hand, where the latter served as a control condition. A certified physiotherapist (CS) carried out all motor assessments. To investigate possible experience-driven functional and structural changes of task-specific neural networks a high-density EEG session and a MRI session were scheduled before and after the training. The high-density EEG session comprised one block of attempted movement (AM), one block of MI and one block of MI EEG-based NF, using the same movement and NF procedure as in the home-based sessions. The MRI session included diffusion weighted imaging as well as structural and functional neuroimaging. EEG and MRI data acquisition parameters are provided as **Supplementary Methods**. The fMRI session comprised one AM and one MI block. For the fMRI session the inter-trial interval was extended to 5 s - 9 s, with steps of 1 s, in order to account for the hemodynamic delay, and stimulus presentation was controlled with Presentation software (Neurobehavioral Systems, Albany, USA). To evaluate the MI training AM-induced fMRI and EEG activity were analysed and diffusion tensor imaging (DTI) analysis conducted. Moreover, we performed lesion mapping. Detailed processing steps are provided in the **Supplementary Methods**. Every session participants were asked to rate the perceived intensity of MI and the support of NF on a 5-point Likert scale as well as their motivation on a visual

analogue scale. Additionally, comments made spontaneously by the patients were recorded.

2.4. Primary and secondary outcome measures

The primary outcome measure, motor function, was assessed with the mFMA and the MAS. In addition, various secondary outcome measures were investigated. Functional changes were evaluated with MI-induced ERD, AM-induced ERD and AM-related sensorimotor BOLD activity. Structural changes were quantified by means of fractional anisotropy (FA) of the cortico-spinal tract (CST). Subjective ratings on motivation and task characteristics, average low-density classification accuracies and patient's comments were jointly considered to judge the feasibility of the NF training protocol. All primary and secondary outcome measures were assessed and evaluated separately for each patient.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

3. Results

3.1. Case 1

P20 was a 71 year old right handed retired female with a right-sided ischemic lesion of the Pons (see Fig. 2A). Time since vascular event was 7 months. Lesion size was 0.37 cm³ and lesion – cortico-spinal tract (CST) overlap was 0.30 cm³, which corresponds to 2.12% of the CST size. Her initial Fugl-Meyer motor assessment (mFMA) score was 52 showing only minor deficits in fine motor skills and minor resistance in wrist and elbow extension resulting in a modified version of the Ashworth scale (MAS) score of 2 in her left, non-dominant hand. Besides the minor motor deficits of the upper limb, P20 did not show additional motor impairments. Self-report revealed an unsteady gait, which was not obvious by observation. After the intervention her mFMA score was 59 and her MAS score 0. P20 was medication free during the study.

P20 had a strong event-related desynchronization (ERD) during motor imagery (MI) of the affected hand, but at the beginning of the training this ERD was stronger on the contralesional side than ipsilesionally. This reversed activity pattern of stronger contralesional than ipsilesional activity is typical for chronic stroke patients and has been described as detrimental (23). Over the training period the lateralization of the ERD for MI of the affected hand (ipsilesional - contralesional) changed significantly (bootstrapping 1000; $p < .01$) towards a stronger ipsilesional than contralesional activity (see Fig. 2C). Pre- and post-training high density electroencephalogram (EEG) showed a similar reversal of laterality of the ERD during attempted movement (AM) (Fig. 2D). Moreover, AM induced stronger lateralization of sensorimotor functional magnetic resonance imaging (fMRI) BOLD activity after the MI training as

1
2
3 compared to before the MI training (Fig. 2E). The increased lateralization was
4
5 attributable to both an increase in ipsilesional and a decreased contralesional activity.
6
7 These functional changes were accompanied by structural changes: the difference in
8
9 white matter integrity between the ipsilesional and the contralesional CST decreased,
10
11 due to an increased fractional anisotropy (FA) in the ipsilesional CST and decreased
12
13 FA in the contralesional CST (Fig. 2E). P20 was highly motivated throughout the
14
15 study, motivation scores showing a positive trend despite slight fluctuations
16
17 (bootstrapping 1000; $p > .1$). Overall she rated the MI as moderately intense and the
18
19 MI neurofeedback (NF) as providing little support. Spontaneously she said, that
20
21 during the MI "... something in my hand was working" and "... my hand got warm,
22
23 because my imagination was so strong." For both NF dimensions high single trial
24
25 classification accuracies were obtained across all training sessions (contralateral ERD:
26
27 $M = 88.79\%$, $SD = 3.48\%$; ERD laterality: $M = 80.39\%$, $SD = 5.55\%$).
28
29
30
31
32
33

34 In summary, motor assessment revealed a clinical relevant increase in mFMA
35
36 scores and a decrease in MAS scores. Moreover, all functional imaging measures
37
38 revealed increased lateralization during MI and AM of the affected hand. Functional
39
40 changes were paralleled by structural changes towards a more balanced white matter
41
42 integrity between left and right CST.
43
44
45
46

47 --- FIGURE 2 HERE ---
48
49
50
51

52 3.2. Case 2

53
54 P21 was a 51 year old right handed male, who was unemployed. He suffered
55
56 from a right-sided basal ganglia hemorrhage 30 months before participation in this
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

study. The size of the lesion was 6.29 cm³ and the overlap between lesion and CST was 1.92 cm³ or 14.1% of the size of the CST (Fig. 3A). His initial mFMA score was 10 resulting from residual shoulder and elbow function and he showed severe spasticity in his paralyzed wrist and elbow joints leading to an MAS score of 8. The stroke resulted in a motor hemiparesis, also causing motor impairments of the lower left limb, although the patient was able to walk unaided. After the intervention his mFMA score was 11 and the MAS score 7. P21 was medication free during the study.

Overall the ERD induced by MI of the affected hand was, when compared to the ERD of P20 and P22, of medium strength and in most training sessions ipsilesional ERD was stronger than contralesional ERD. Over the course of MI training, the ERD lateralization increased, although this increase was not significant (bootstrapping 1000; $p > .1$, see Fig. 3C). Moreover, P21 showed strong intra-individual variability in ERD lateralization across MI sessions. A pre-post comparison of high-density EEG activity of AM indicated stronger ERD after the training (Fig. 3D), while retaining a comparable level of ERD lateralization. On the other hand sensorimotor fMRI activity induced by AM was slightly increased after the training in the ipsilesional hemisphere, but remained unchanged in the contralesional hemisphere, resulting in a small increase in lateralization (Fig. 3E). White matter integrity of the contralesional CST was also unchanged between the pre- and post assessment, FA of the ipsilesional CST was found to be minimally decreased after the MI training (Fig. 3E). P21 was highly motivated throughout the study and motivation scores showing a positive trend (bootstrapping 1000; $p > .1$). Overall he rated the MI as intense and said spontaneously "... a warm flow in the hand." and "... a tingling in my hand, as if someone strokes the skin with a brush." The NF was rated as very supportive and

spontaneously described as “Great to see: I moved something!” and “This spurs me on!”. For both NF dimensions moderate single trial classification accuracies were obtained across all training sessions (contralateral ERD: $M = 63.51\%$, $SD = 5.53\%$; ERD laterality: $M = 69.03\%$, $SD = 4.33\%$).

In sum, behavioral outcomes indicate a minor increase in mFMA scores as well as a small decrease in MAS scores. MI induced an ERD of medium strength, which fluctuated largely over the course of training. The small changes observed on functional and structural level are not necessarily facing the same direction.

--- FIGURE 3 HERE ---

3.3. Case 3

Participant P22 was a 56 year old male, retired since the vascular event. He was diagnosed with an ischemic, left-sided infarction of the medial and anterior cerebral arteries resulting in right-sided hemiparesis (Fig. 4A), i.e., on his premorbidly dominant side. The lesion size was 125.63 cm^3 and the lesion – CST overlap was 1.31 cm^3 or 9.64% of the size of the CST. The stroke occurred 55 months prior to onset of the study. His initial mFMA score was 3 resulting from residual shoulder function and his MAS score was 8, showing severe motor deficits and high spasticity in his wrist and elbow joints. He was able to walk independently despite the lower limb paresis. Furthermore, he showed an aphasia, which did not affect his understanding or performance of the tasks. Following the intervention his mFMA and MAS score were unchanged. P22 was on medication during the study (**Supplemental Material**).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

During MI of the affected hand P22 showed a strong ERD, which was in all training sessions stronger over the ipsilesional hemisphere than over the contralesional hemisphere. During the training a trend for significantly increased MI-induced ERD lateralization (bootstrapping 1000; $p < .06$) could be observed (Fig. 4C). In contrast to MI, AM of the affected hand was related to a very small, hardly visible, ERD (Fig. 4D). No changes in AM-related ERD strength or lateralization between the two different times of measurement were observed, although fMRI sessions revealed increased sensorimotor BOLD activity for both hemispheres (Fig. 4E). In line with fMRI changes, increased FA could be observed for both CSTs (Fig. 4E). P22 was highly motivated throughout the study, although his motivation seemed to be higher in the first half (bootstrapping 1000; $p > .1$). On average he rated the MI as intense and the NF as supportive, spontaneously he said: “The feedback blocks are less effortful than the blocks without feedback.” For both NF dimensions good single trial classification accuracies were obtained across all training sessions (contralateral ERD: $M = 78.19\%$, $SD = 8.57\%$; ERD laterality: $M = 75.47\%$, $SD = 3.98\%$).

Taken together, no changes in motor function, as assessed by the mFMA and MAS, could be observed. MI of the affected hand was related to strong ERD, whereby the ERD lateralization increased over the course of training. AM induced only a very subtle ERD and BOLD activity, however while ERD remained unchanged, fMRI activity was found to be increased after the MI training. On the structural level an increase in white matter integrity was found.

--- FIGURE 4 HERE ---

4. Discussion

We examined the feasibility of conducting long-term motor imagery (MI) electroencephalogram (EEG)-based neurofeedback (NF) training at three stroke patients' homes and explored possible improvements on upper limb motor functioning. The protocol was employed in three chronic stroke patients with different lesion types and residual movement capacity. Training effects were evaluated by detailed motor assessment. Moreover, several secondary outcome measures were applied, including MI-induced event-related desynchronization (ERD), attempted movement (AM)-induced ERD, functional magnetic resonance imaging (fMRI) BOLD activity and structural changes of cortico-spinal tract (CST) white matter integrity. Over the course of MI EEG-based NF training a remarkable increase in EEG lateralization during MI of the affected hand was observed in one patient (P20), with a smaller, yet non-significant increase in the other two patients (P21, P22). In one patient (P20) the EEG lateralization increase was accompanied by an increased lateralization of fMRI activity, a re-balanced CST integrity and improved motor abilities.

A key primary objective of this study was to investigate the feasibility of this training regime and identify potential problems of regular home-based MI NF training for stroke patients with chronic motor impairments. Specifically, we expected potential disturbances in executing the training due to daily life demands, the cognitive demands of this NF implementation and potential interferences of the home based setting on EEG recording quality. Overall we noted a very positive response to the training. Comments that were made spontaneously by patients indicated that they liked the training and the challenge associated with it. Moreover, they did not report

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

adverse effects of the EEG application and that did not struggle with the demanding training regime. All three individuals were very motivated, cooperative, and able to perform MI and to process the NF. Although this observation seems to be consisted across several patient characteristics, e.g. age and severity of motor disabilities, future investigations need to evaluate the applicability of this NF protocol for stroke patients with cognitive deficits. Moreover, **as evaluated by visual inspection of the EEG raw data**, good EEG data quality was obtained at the patients' homes. Taken together, this provides solid evidence that frequent home-based MI NF training in patients with chronic motor disabilities is feasible.

Over the course of training changes in cortical activation related to MI of the affected hand were observed **on a descriptive level** in all three patients. Specifically, an increase in lateralization was evident. Increased activity in sensorimotor regions of the contralesional hemisphere related to movement attempts of the paretic limb has been frequently documented after stroke (11,23,24,27–31). Moreover, the resulting reduction in cortical lateralization has been related to poor recovery (23). Along the same lines, shifts in laterality towards an increased ratio of ipsilesional to contralesional sensorimotor cortex activity have been related to changes in behavioural performance (11,32). In our study, the patient with the strongest change in lateralization over the course of the training also showed **significant** motor improvement. **In addition**, ERD and fMRI BOLD activity induced by AM were more lateralized after than before the training. Finally, white matter integrity of the ipsilesional and contralesional CST were less distinct after the training. These functional and structural changes accompanied clinically relevant improvement of motor functions. In the absence of a control group we cannot argue for a causal

relationship between MI training and the observed functional, structural and behavioural changes, but our results clearly suggest that the employed training contributed to adaptive reorganization and motor recovery in this case. To which extent the observed recovery-related changes are due to the MI training, physical therapy or other factors remains speculative. For the two more severely affected patients, the training resulted only in changes on the descriptive level and no behavioural improvement could be observed. It is conceivable that the necessary amount of training to achieve clinically relevant changes is related to the degree of motor impairment. It could also be argued, that due to location and size of the lesion, or the overlap between lesion and CST, those patients are less likely to benefit from this type of training. However, all patients had preserved CST fibres and were able to imagine the instructed movement and both aspects seem necessary for MI training to be effective. Moreover, it is conceivable that a flexible training regime that is to some degree adapted to each patient leads to stronger improvements. Individually tailored training may include individualized hard- and software, e.g. EEG caps (33) and NF parameters (34), as well as an individualized training plan, which comprises not only the frequency of training, but also the time of day at which it is conducted, the type and modality of feedback or the imagined movements.

The main objective of the pre-post measurements was to investigate in depth the effects of home-based MI neurofeedback training. Particular emphasis was placed on evaluating the effects of MI NF training on the neural signatures of MI using high-density EEG and fMRI, and on evaluating if these effects transfer to physically executed movements. Broadly speaking, the cortical lateralization of movement-related activity assessed during the training sessions, pre-post fMRI and pre-post

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

high-density EEG did not only yield converging results. Some discrepancies might originate from differences between MI and AM, differences in hemodynamic and electrophysiological recordings and normal variation that occurs between sessions. Regarding the first of these three aspects, MI was practiced during the training sessions and transfer effects on AM were evaluated in the pre-post comparison. Yet MI and AM activation patterns differ to some degree (35), hence care should be taken when comparing the neuronal correlates of the training sessions and the pre-post measurements. The rehabilitative potential of MI training depends, among other factors, on a better understanding of the transfer from mentally practiced movements to overt physical performance. On the second aspect, we recently revealed a clear and consistent dissociation between hemodynamic and electrophysiological signatures regarding ME- and MI-induced cortical lateralization using concurrent EEG-fMRI and EEG-fNIRS recordings (17,36,37). These indicate that lateralization patterns obtained in one imaging modality cannot be easily transferred to a second independent imaging modality and may contribute to the dissociation between fMRI BOLD activity and ERD measures obtained in the present investigation. This illustrates how important multimodal neuroimaging studies are to develop a comprehensive picture of functional recovery. In addition, the intra-individual variance that was evident in the training sessions highlights the importance of permanent monitoring. Rehabilitation progress should be assessed based on performance trends and not only on single sessions, such as pre-post comparisons, as the latter can be strongly influenced by intra-individual variance in performance. For these reasons, direct comparisons between sessions and imaging modalities should be made cautiously.

For Peer Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

5. Conclusion

This work demonstrates for the first time that frequent home-based motor imagery (MI) electroencephalogram (EEG)-based neurofeedback (NF) training is feasible in chronic stroke patients. First anecdotal evidence also indicates that our training regime **has the potential to** facilitate behavioural, functional and structural changes. Future research will be required to optimize the training regime and verify its effectiveness in a proper clinical trial study. How long-lasting the effects of high intensity MI NF training are needs to be determined as well.

Declaration of interest

The authors declare that there is no conflict of interest.

For Peer Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. Jones TA, Adkins DL. Motor System Reorganization After Stroke: Stimulating and Training Toward Perfection. *Physiology (Bethesda)* [Internet]. 2015;30(5):358–70. Available from: <http://physiologyonline.physiology.org.offcampus.dam.unito.it/content/30/5/358.long>
2. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197–223.
3. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Anderson CS. Long-Term Disability After First-Ever Stroke and Related Prognostic Factors in the Perth Community Stroke Study ,. 2016;1989–90.
4. Jeannerod M. Neural simulation of action: a unifying mechanism for motor cognition. *Neuroimage*. 2001 Jul;14:103–9.
5. Cicinelli P, Marconi B, Zaccagnini M, Pasqualetti P, Filippi MM, Rossini PM. Imagery-induced cortical excitability changes in stroke: A transcranial magnetic stimulation study. *Cereb Cortex*. 2006;16(2):247–53.
6. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol*. Elsevier Ltd; 2009 Aug;8(8):741–54.
7. Page SJ, Levine P, Leonard AC. Effects of mental practice on affected limb use and function in chronic stroke. *Arch Phys Med Rehabil*. 2005 Mar;86(3):399–402.
8. Crosbie JH, McDonough SM, Gilmore DH, Wiggam MI. The adjunctive role of mental practice in the rehabilitation of the upper limb after hemiplegic stroke: a pilot study. *Clin Rehabil*. 2004 Feb;18(1):60–8.
9. Liu KP, Chan CC, Lee TM, Hui-Chan CW. Mental imagery for promoting relearning for people after stroke: a randomized controlled trial. *Arch Phys Med Rehabil*. 2004 Sep;85(9):1403–8.
10. Grosse-Wentrup M, Mattia D, Oweiss K. Using brain-computer interfaces to induce neural plasticity and restore function. *J Neural Eng*. 2011;8(2):25004.
11. Buch E, Weber C, Cohen LG, Braun C, Dimyan M a, Ard T, et al. Think to move: a neuromagnetic brain-computer interface (BCI) system for chronic stroke. *Stroke*. 2008 Mar;39(3):910–7.

12. Broetz D, Braun C, Weber C, Soekadar SR, Caria A, Birbaumer N. Combination of brain-computer interface training and goal-directed physical therapy in chronic stroke: a case report. *Neurorehabil Neural Repair*. 2010 Sep;24(7):674–9.
13. Caria A, Weber C, Brötz D, Ramos A, Ticini LF, Gharabaghi A, et al. Chronic stroke recovery after combined BCI training and physiotherapy: a case report. *Psychophysiology*. 2011 Apr;48(4):578–82.
14. Ramos-Murguialday A, Broetz D, Rea M, Lärer L, Yilmaz Ö, Brasil FL, et al. Brain-machine interface in chronic stroke rehabilitation: A controlled study. *Ann Neurol*. 2013;74(1):100–8.
15. Shindo K, Kawashima K, Ushiba J, Ota N, Ito M, Ota T, et al. Effects of neurofeedback training with an electroencephalogram-based brain-computer interface for hand paralysis in patients with chronic stroke: a preliminary case series study. *J Rehabil Med*. 2011;43(10):951–7.
16. Pichiorri F, Morone G, Petti M, Toppi J, Pisotta I, Molinari M, et al. Brain-computer interface boosts motor imagery practice during stroke recovery. *Ann Neurol*. 2015;77(5):851–65.
17. Zich C, Debener S, Kranczioch C, Bleichner MG, Gutberlet I, De Vos M. Real-time EEG feedback during simultaneous EEG-fMRI identifies the cortical signature of motor imagery. *Neuroimage*. 2015;114:438–47.
18. Debener S, Minow F, Emkes R, Gandras K, De Vos M. How about taking a low-cost, small, and wireless EEG for a walk? *Psychophysiology*. 2012 Nov;49(11):1617–21.
19. Kranczioch C, Zich C, Schierholz I, Sterr A. Mobile EEG and its potential to promote the theory and application of imagery-based motor rehabilitation. *Int J Psychophysiol*. 2014;91(1):10–5.
20. De Vos M, Kroesen M, Emkes R, Debener S. P300 speller BCI with a mobile EEG system: comparison to a traditional amplifier. *J Neural Eng*. 2014 Jun;11(3):36008.
21. Debener S, Emkes R, De Vos M, Bleichner M. Unobtrusive ambulatory EEG using a smartphone and flexible printed electrodes around the ear. *Sci Rep*. Nature Publishing Group; 2015;5:16743.
22. Renard Y, Lotte F, Gibert G, Congedo M, Maby E, Delannoy V, et al. OpenViBE : An Open-Source Software Platform to Design , Test , and Use

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Brain – Computer Interfaces in Real and Virtual. Presence. 2010;19(1):35–53.

23. Ward NS, Brown MM, Thompson AJ, Frackowiak RSJ. Neural correlates of outcome after stroke: A cross-sectional fMRI study. Brain. 2003;126(6):1430–48.

24. Ward NS, Brown MM, Thompson AJ, Frackowiak RSJ. Neural correlates of motor recovery after stroke: A longitudinal fMRI study. Brain. 2003;126(11):2476–96.

25. Fugl-Meyer AR, Jääskö L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scand J Rehabil Med [Internet]. 1975 [cited 2016 Aug 29];7(1):13–31. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1135616>

26. Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. Clin Rehabil [Internet]. 1999 Oct [cited 2016 Aug 29];13(5):373–83. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10498344>

27. Johansen-Berg H, Rushworth MFS, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM. The role of ipsilateral premotor cortex in hand movement after stroke. Proc Natl Acad Sci U S A. 2002 Oct 29;99(22):14518–23.

28. Feydy A, Carlier R, Roby-Brami A, Bussel B, Cazalis F, Pierot L, et al. Longitudinal Study of Motor Recovery After Stroke: Recruitment and Focusing of Brain Activation. Stroke. Lippincott Williams & Wilkins; 2002 Jun 1;33(6):1610–7.

29. Cramer SC, Nelles G, Benson RR, Kaplan JD, Parker RA, Kwong KK, et al. A Functional MRI Study of Subjects Recovered From Hemiparetic Stroke. Stroke. Lippincott Williams & Wilkins; 1997 Dec 1;28(12):2518–27.

30. Chollet F, DiPiero V, Wise RJ, Brooks DJ, Dolan RJ, Frackowiak RS. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. Ann Neurol. 1991 Jan;29(1):63–71.

31. Caramia MD, Iani C, Bernardi G. Cerebral plasticity after stroke as revealed by ipsilateral responses to magnetic stimulation. Neuroreport. 1996;7(11):1756–60.

32. Calautti C, Leroy F, Guincestre JY, Marié RM, Baron JC. Sequential activation brain mapping after subcortical stroke: changes in hemispheric balance and

- recovery. *Neuroreport* [Internet]. 2001 Dec 21 [cited 2016 Aug 29];12(18):3883–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11742203>
33. Zich C, De Vos M, Kranczioch C, Debener S. Wireless EEG with individualized channel layout enables efficient motor imagery training. *Clin Neurophysiol. International Federation of Clinical Neurophysiology*; 2015;126(4):698–710.
34. Blankertz B, Losch F, Krauledat M, Dornhege G, Curio G, Müller K-R. The Berlin Brain-Computer Interface: accurate performance from first-session in BCI-naïve subjects. *IEEE Trans Biomed Eng*. 2008 Oct;55(10):2452–62.
35. Blokland Y, Spyrou L, Thijssen D, Eijssvogels T, Colier W, Floor-Westerdijk M, et al. Combined EEG-fNIRS decoding of motor attempt and imagery for brain switch control: An offline study in patients with tetraplegia. *IEEE Trans Neural Syst Rehabil Eng*. 2014;22(2):222–9.
36. Zich C, Debener S, Kranczioch C, Chen L-C, De Vos M. Lateralization patterns for movement execution and imagination investigated with concurrent EEG-fMRI and EEG-fNIRS. In: Müller-Putz GR, Huggins JE, Steyrl D, editors. *Proceedings of the Sixth International Brain-Computer Interface Meeting: BCI Past, Present, and Future*. Pacific Grove, California, USA: Verlag der Technischen Universität Graz; 2016. p. 101.
37. Zich C, Debener S, Thoene A-K, Chen L-C, Kranczioch C. Simultaneous EEG-fNIRS reveals how age and feedback affect motor imagery signatures. *Neurobiol Aging*. 2017;49:183–97.

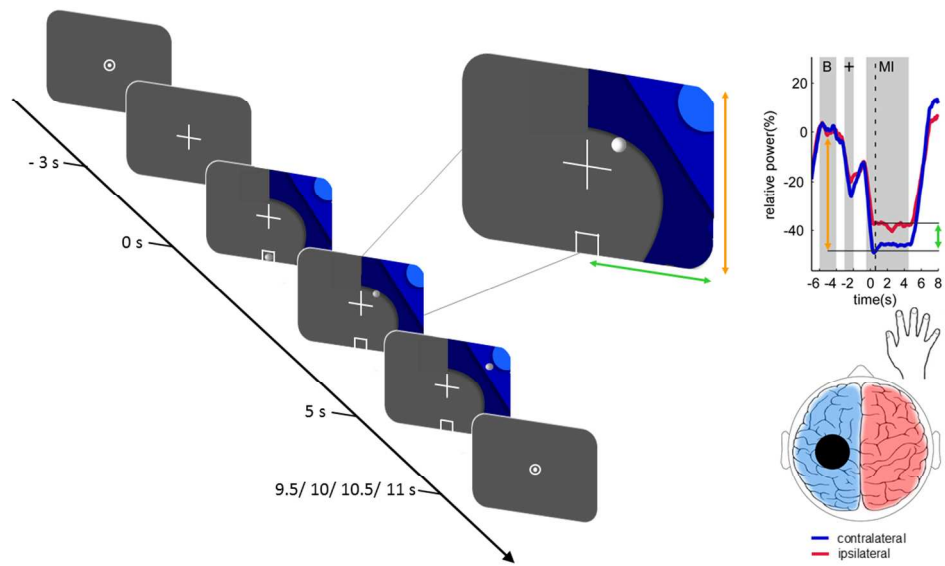


Fig. 1 Trial structure and relationship between the two-dimensional NF display and MI-induced brain activity. The trial structure is illustrated exemplary for a right hand trial. Each trial was initiated with a fixation-cross and after a delay of 3 s a graphic comprising three different shades of blue was added. Onset of the graphic indicated the beginning of the task period (duration 5 s). The location of the graphic indicated which hand to use. During the NF blocks a white circle resembling a ball moved along the horizontal (green arrow) and vertical (orange arrow) axes according to the classifier output magnitudes. Trials were followed by fixation dot, resulting in an inter-trial interval of 4.5 s to 6 s. The relationship between the position of the ball and the MI-induced brain activity at the time point of the dashed vertical line is illustrated on an exemplary ERD time course. The horizontal ball position is determined by the classification of MI contralateral (blue) versus ipsilateral (red), as illustrated by the green arrow. The vertical ball position is determined by the classification of contralateral baseline ('B') versus contralateral MI, as illustrated by the orange arrow.

338x190mm (96 x 96 DPI)

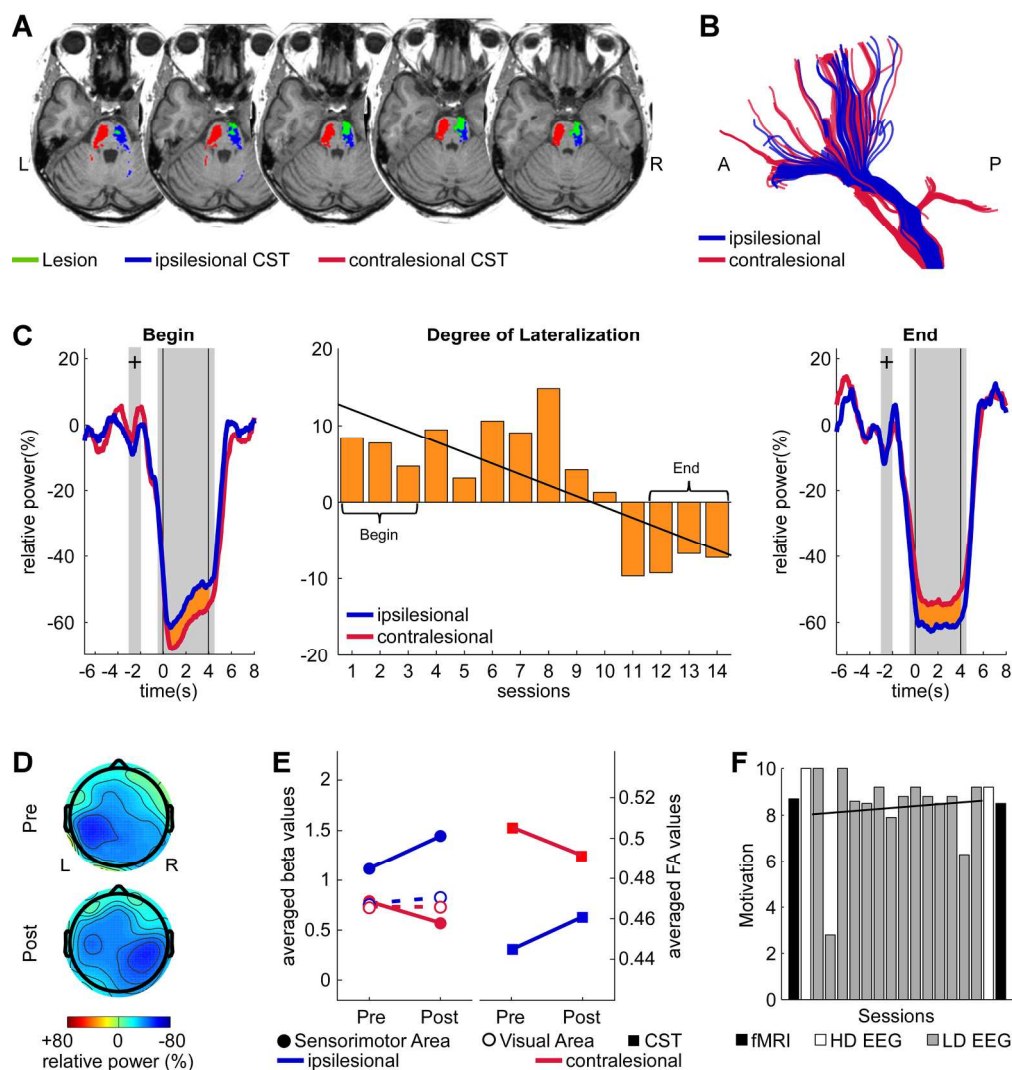


Fig. 2 Lesion characteristics and secondary outcome measures P20. (A) Individual lesion map (green) overlaid onto anatomical (Johns Hopkins University (JHU) White-Matter Tractography Atlas) ipsilesional CST (blue) and contralesional CST (red). The axial slices depicted correspond to $z = 21, 22, 23, 24$ and 25 in MNI space. (B) DTI based reconstruction of individual ipsilesional (blue) and contralesional (red) CST fibers illustrated in the sagittal view. (C) ERD related to MI of the affected hand over the training period. Time course of relative power in % induced by MI averaged for the first three (left) and last three (right) trainings sessions. Means for the ipsilesional hemisphere are visualized in blue and for the contralesional hemisphere in red. The first grey shaded area indicates the time window of fixation cross onset, and the second grey shaded area indicates the time window of MI. The two vertical lines indicate the interval (0.5 to 4.5 s) used to extract the lateralization parameter (contralateral - ipsilateral ERD) illustrated in the middle. Data from the two NF blocks were averaged. (D) Topography of ERD induced by AM of the affected hand before (top) and after (bottom) the MI training assessed with high-density EEG. (E) fMRI activity (left) and averaged FA values (right) measured before and after the MI training. fMRI BOLD activity during AM extracted from ipsi- (blue) and contralesional (red) anatomical region of interests. Brodmann areas 1, 2, 3 & 4 were regions of interest (coloured circles, solid lines) and Brodmann areas 17 and 18 as control regions (open circles, dashed line). Averaged FA values extracted from individuals contra- (blue) and ipsilesional (red) CST fibers. (F) Motivation scores obtained on fMRI, high-density (HD) EEG and low-density (LD) EEG sessions. Regression lines are fitted for the low-density EEG sessions.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

198x209mm (300 x 300 DPI)

For Peer Review

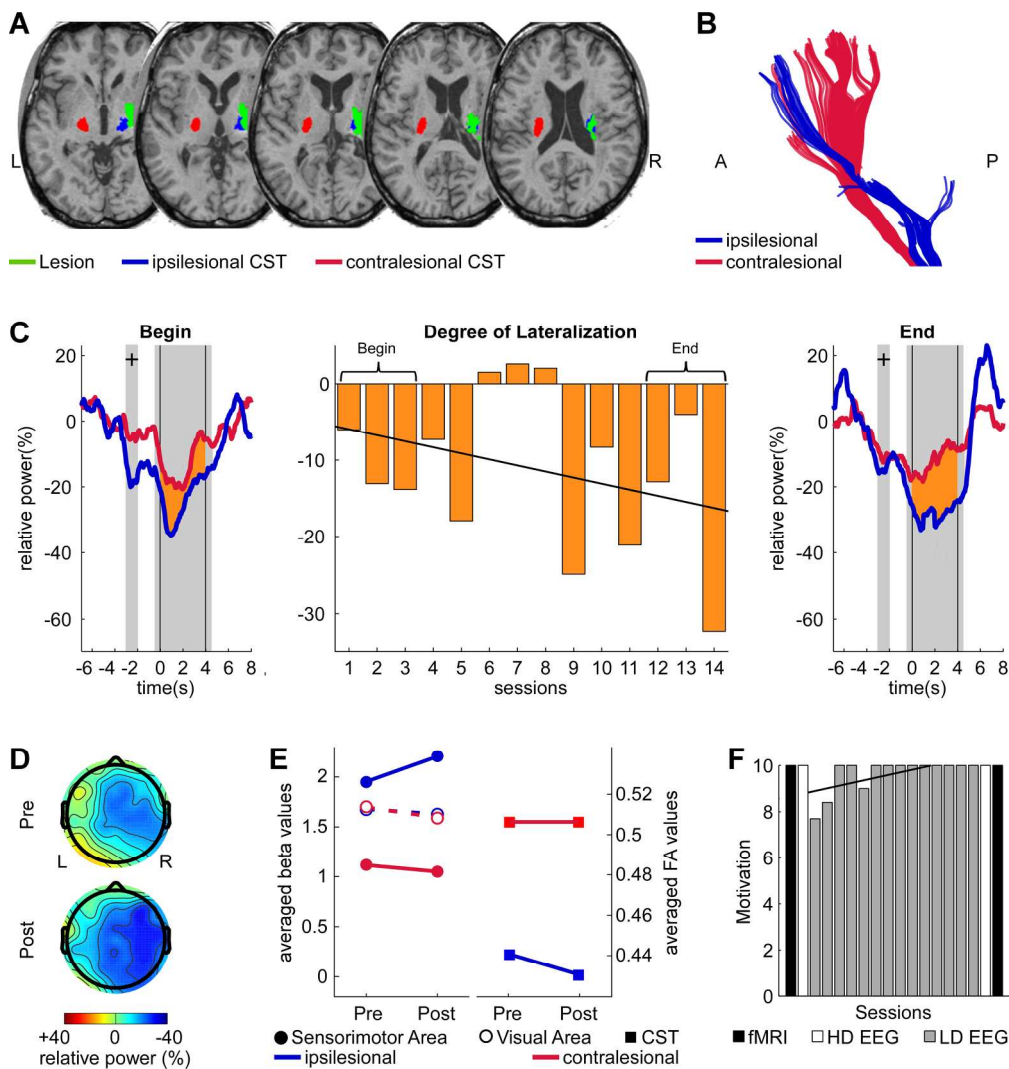


Fig. 3 Lesion characteristics and secondary outcome measures P21. As Fig. 2, but (A) shows the axial slices corresponding to z = 47, 52, 57, 62 and 67 in MNI space.

199x211mm (300 x 300 DPI)

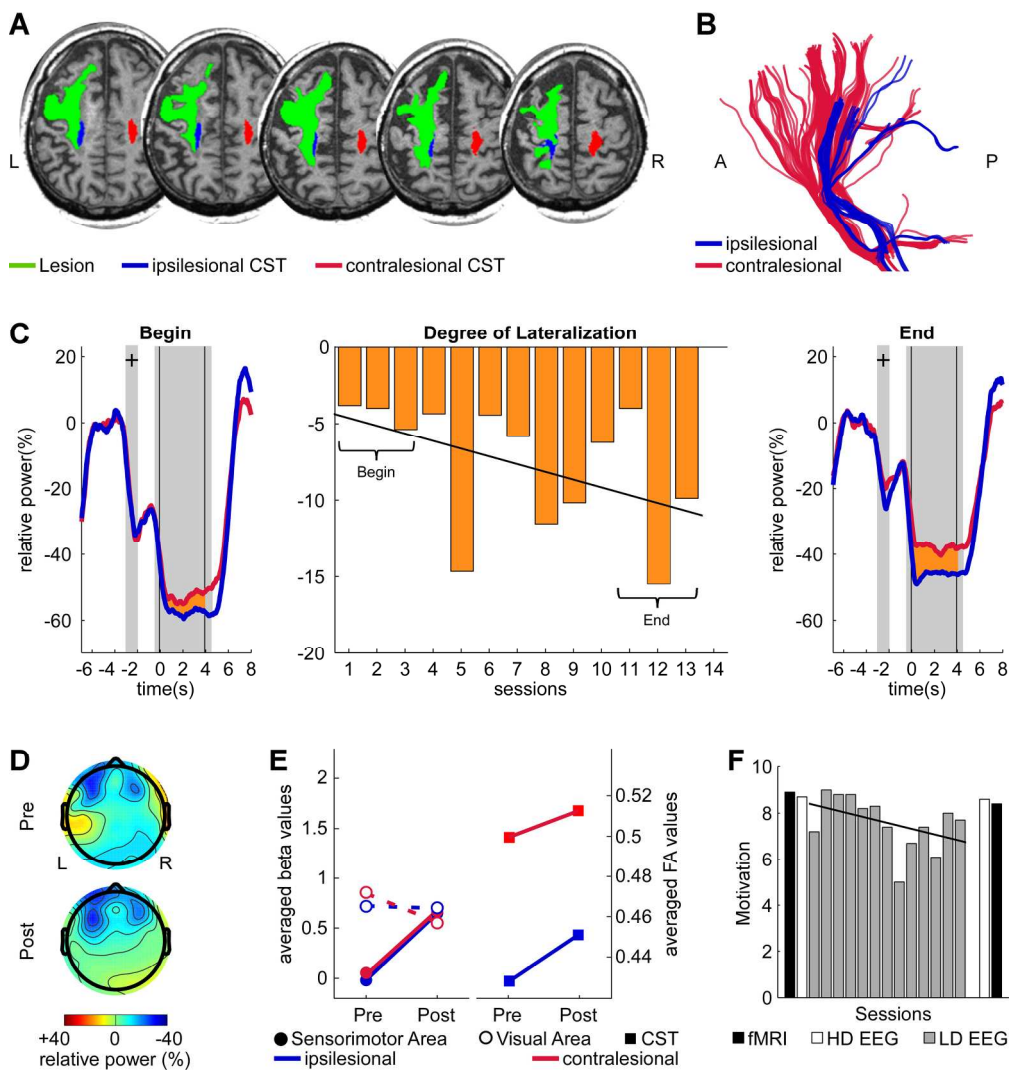


Fig. 4 Lesion characteristics and secondary outcome measures P22. As Fig. 2, but (A) shows the axial slices corresponding to $z = 90, 94, 98, 102$ and 106 in MNI space.

198x209mm (300 x 300 DPI)

**Supplemental Material for “High intensity chronic stroke motor imagery
neurofeedback training at home - three case reports”**

For Peer Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Supplementary Methods

Self-paced break

To further enhance the user-friendliness of the neurofeedback implementation, patients could initiate 10-second breaks. Breaks could be started in every inter-trial interval via a foot pedal. When a break was initiated a thermometer-like scale consisting of 10 segments was displayed. Every second one segment of the bar changed color from white to gray to visualize the passing of time. After the break the experiment continued with a new inter-trial interval.

Mobile EEG – Data Acquisition

The EEG system used is made up of 24 Ag/AgCl electrodes (Fp1, Fp2, Fz, F7, F8, Fc1, Fc2, Cz, C3, C4, T7, T8, Cpz, Cp1, Cp2, Cp5, Cp6, Tp9, Tp10, Pz, P3, P4, O1, O2, with Afz as ground and Fcz as reference, Easycap, Herrsching, Germany) and a small, wireless, head-mounted amplifier (mBrainTrain, Belgrade, Serbia). Data were recorded with a resolution of 24 bits and a sampling rate of 500 Hz and transmitted wirelessly via bluetooth to OpenVibe Acquisition Server 1.0.1 (1).

Mobile EEG – Online Data Analysis for neurofeedback

EEG data were analyzed online to provide real-time NF and analyzed offline for subsequent analysis. Online analysis consisted of two parts. The first part of the online analysis was performed between blocks, specifically before the second and before the third MI block, using OpenViBE and EEGLAB. Here, parameters for the NF were derived (2). The second part of the online analysis consisted of the actual real-time NF delivery through OpenViBE Designer 0.17.1 (1). For realization of the first part, EEG data from the just completed MI block were high-pass filtered at 8 Hz (finite impulse response, filter order 826) and subsequently low-pass filtered at 30 Hz (finite impulse response, filter order 220) using EEGLAB. MI intervals were extracted from 0.5 to 4.5 s after the onset of MI, and segments containing artefacts were rejected (EEGLAB function pop_jointprob.m, SD = 3). For the band-pass filtered data subject-specific spatial filters were calculated using a common spatial pattern (CSP) implementation (3). The use of CSP enhances the signal-to-noise ratio and account for inter-individual differences in the neurophysiological data, why CSP is presently considered as the state-of-the-art spatial filter in MI NF or brain computer

interface implementations (4). The CSP approach maximizes the variance of the signals of a first class (e.g. left hand MI) while minimizing the variance of the signal of a second class (e.g. right hand MI) and vice versa in a computationally efficient way. The outcome of the CSP is a square matrix (spatial filter x channels), that is, there are as many spatial filters as there are channels. The first spatial filter in the matrix explains most of the variance for the first class and the last spatial filter in the matrix explains most of the variance for the second class, the second and next-to-last filters explain the second most variance and so on. For the NF implementation used in the present study two spatial filters were selected, one for left and one for right hand MI. Choice was based on maximum variance segregation and neurophysiological plausibility (5). Specifically, the three spatial filters maximally contributing to variance segregation per class were visually evaluated and for each class the spatial filter with the highest neurophysiological plausibility was selected. Neurophysiological plausibility was defined as lateralized activation patterns over sensorimotor areas. In order to provide NF based on subject-specific spatial information, the coefficients of the two selected spatial filters were passed on to OpenViBE. Here again, raw data obtained in the previous block were temporally filtered between 8 and 30 Hz in OpenViBE. Data were then spatially filtered and segmented into baseline (7 s to 3 s before graphic onset) and MI intervals (0.5 s to 4.5 s after graphic onset) for right and left hand separately. These intervals were subdivided into 56 consecutive bins, each bin consisted of a moving average of 1 s width, shifted in time by 62.5 ms. The binning procedure is the standard approach in the implementation of the Graz MI protocol in OpenVibe and it is widely used in MI NF (1,6–8). Logarithmic power of the band-pass filtered data of 1 s time windows represented the features for linear discrimination analysis (LDA) classification (9). In total three LDA-based classification processes were performed: Classification of contralateral activity during the MI interval versus contralateral baseline, separately for left and right hand MI, and classification of contra- versus ipsilateral activity in the MI interval. In all three cases the mean classification from a seven-fold cross-validation procedure was computed. Based on the results of the cross-validation three border values were calculated corresponding to the upper quartiles of the three classification distributions. These border values were used to set the range of the display for the online NF of the subsequent block. In order to increase motivation negative NF was avoided.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

The second part of the online analysis incorporated the delivery of real-time NF in the two NF blocks. Incoming data were temporally (8-30 Hz) and spatially (CSP) filtered. Features were then extracted as described for the first part of the online analysis and classified. For each time bin two classification processes were than performed simultaneously: Classification of contralateral activity during the MI interval versus baseline and classification of contra- versus ipsilateral activity in the MI interval. The classification outputs were translated into the vertical and horizontal positions of a ball displayed in the NF graphic.

Mobile EEG – Offline Data Analysis

For offline analysis EEG raw data of the two NF blocks were high-pass filtered at 1 Hz (finite impulse response, filter order 1650) and subsequently low-pass filtered at 40 Hz (finite impulse response, filter order 166). Filtered data were segmented into consecutive time intervals of 1 s. Segments containing artefacts were rejected (EEGLAB functions pop_jointprob.m, pop_rejkurt.m, both SD = 3). Remaining data were submitted to extended infomax ICA (10) to estimate the unmixing weights of 24 independent components. Components representing stereotypical artefacts such as eye-blinks, eye-movements and electrical heartbeat activity were identified and removed from the raw data. These corrected data were then high-pass filtered at 8 Hz and subsequently low-pass filtered at 30 Hz (finite impulse response, filter order 825 and 220, respectively). EEG data were segmented (-7 s to 9 s relative to the onset of the graphic) and any segments with residual artefacts were rejected (EEGLAB functions pop_jointprob.m, pop_rejkurt.m, both SD = 3). ERD was calculated for each sensor as follows: $ERD\%(t) = (A(t) - R) / R \times 100$, where R is the power of a 2 s baseline interval before fixation-cross onset (-5.5 s to -3.5 s relative to the onset of the graphic), and A is the power at time point t, with t=0 indicating the onset of MI (11). ERD was extracted from a left (C3, Cp1, CP5 and P3) and a right (C4, Cp2, Cp6 and P4) sensorimotor region of interest (ROI). For the statistical analysis of EEG data ERD was averaged within the ROIs and across a time window covering 0.5 s to 4.5 s with respect to the onset of the graphic.

High-density EEG – Data Acquisition

High-density EEG data were acquired from 96 equidistant scalp sites using Ag/AgCl electrodes with a central fronto-polar site as ground and the nose-tip as reference (Easycap, Herrsching, Germany) and BrainAmp amplifiers (BrainProducts GmbH, Gilching, Germany) in the laboratory. Data were recorded with a sampling rate of 500 Hz with online analog filter settings of 0.015-250 Hz.

High-density EEG – Offline Data Analysis

Offline analysis of high-density EEG data followed exactly the same procedure as the offline analysis of low-density EEG data.

MRI – Data Acquisition

Data acquisition was performed on a 3T Siemens MAGNETOM Verio MRI scanner (Siemens AG, Erlangen, Germany) using the standard twelve-channel head matrix coil. Diffusion weighted images were acquired along 20 directions ($b = 1000 \text{ s/mm}^2$, 49 slices, voxel size $1.8 \times 1.8 \times 2.0 \text{ mm}^3$, $TR = 7100 \text{ ms}$, $TE = 95 \text{ ms}$). Following a high-resolution structural volume was obtained using a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence ($TR = 1900 \text{ ms}$, $TE = 2.52 \text{ ms}$, $FoV = 256 \times 256 \text{ mm}^2$, Flip Angle = 9° , slice thickness = 1 mm , sagittal). During functional measures 310 T2-weighted gradient echo planar imaging volumes ($3.1 \times 3.1 \times 3.1 \text{ mm}$ voxels, 0.75 mm gap, $TR = 2.0 \text{ s}$, $TE = 30 \text{ ms}$, $FoV = 200 \times 200 \text{ mm}^2$, Flip Angle = 80° , 30 transversal slices) were obtained within each block.

Lesion Mapping

Lesions were defined in the spatially normalized T1-weighted images using MRICron (12). In case of marked ventricular dilatation the dilated ventricle was not included in the lesion area. A single rater (CZ) outlined lesions manually. Lesion size is specified in cm^3 . Moreover, the overlap of lesion and corticospinal tract (CST) was calculated. We abstained from using patients' CSTs because they are often damaged as a consequence of the stroke. Instead, CSTs were created based on the Johns Hopkins University (JHU) White-Matter Tractography Atlas (13,14). In order to remove extraneous fiber projections, all tracts were thresholded at 10%. Thresholded tracts were binarized. Lesion – CST overlap was specified in cm^3 and as percentage of the whole CST.

FMRI – Data Analysis

FMRI data were processed and analyzed using SPM8 (FIL, Wellcome Trust Center for Neuroimaging, UCL, London, UK). To correct for head motion the functional time series of each block were realigned to the first image. The structural T1-weighted volume was registered to the mean functional image and segmented, in order to normalize functional and structural images to the Montreal Neurological Institute (MNI) template brain. Finally, normalized functional volumes were smoothed with a three-dimensional Gaussian kernel of 8 mm full-width-half-maximum (FWHM). Single subject models contained two regressors of interest, BOLD response to right and left trials. In addition, six movement parameters representing signal changes related to head movement as calculated in the SPM8 realignment procedure were included. Time series in each voxel were high-pass filtered to 1/128 Hz and modeled for temporal autocorrelation across scans with an AR(1) process. fMRI BOLD activity was quantified as average beta values of all voxels within a ROI. ROIs were defined anatomically. The sensorimotor ROI comprised the primary somatosensory and primary motor cortex (Brodmann areas 1, 2, 3 & 4) and the control ROI consist of the primary and secondary visual cortex (Brodmann areas 17 and 18). fMRI BOLD activity related to attempted movements of the affected hand was extracted from the sensorimotor ROI and the control ROI of the ipsilesional and contralesional hemisphere.

DTI – Data Analysis

Diffusion weighted imaging data were processed and analyzed with ExploreDTI (15). Data were visually inspected for large signal dropouts, geometric distortions and subtle system drifts. Moreover, we checked the difference between the measured and the modeled signal by means of the residual map (16). To correct for subject motion and eddy current induced geometric distortions the diffusion weighted images were realigned to the nondiffusion images (b0-image) using an affine coregistration method (17). The diffusion tensor model was estimated using a nonlinear least squares (Levenberg-Marquardt) algorithm. Subsequently, the fractional anisotropy (FA), ranging from 0 (maximal isotropic diffusion) to 1 (maximal anisotropic diffusion) were calculated. Whole brain tractography was performed (18) using a 1-mm step size. The thresholds to initiate and continue fiber propagation were set to $FA > 0.2$ and tract-turning angle $< 30^\circ$. The CSTs were then reconstructed using two ROIs, the

posterior limb of the upper internal capsule and the lower pons (19), manually drawn by on the directionally color-encoded FA map. Fibers intersecting both ROIs were retained for further analysis, whereby fibers continuing into the other hemisphere were removed. The FA was derived for each CST separately.

Medication P22

ASS 100 mg	0-1-0
Simva Hexal 40 mg	0-0-1
Metformin 1000 mg	1-0-1
Micardis 40 mg	1-0-0
Mirtazapin 15 mg	0-0-0-1
Glimepirid 3,5 mg	1-0-1
Baclofen 10 mg	1-1-0-1
Clopidogrel 75 mg	1-0-0
Zentiva 750 mg	1-0-1

References

1. Renard Y, Lotte F, Gibert G, Congedo M, Maby E, Delannoy V, et al. OpenViBE : An Open-Source Software Platform to Design , Test , and Use Brain – Computer Interfaces in Real and Virtual. Presence. 2010;19(1):35–53.

2. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods. 2004;134(1):9–21.

3. Ramoser H, Müller-Gerking J, Pfurtscheller G. Optimal spatial filtering of single trial EEG during imagined hand movement. IEEE Trans Rehabil Eng. 2000 Dec;8(4):441–6.

4. Blankertz B, Tomioka R, Lemm S, Kawanabe M, Müller K-R. Optimizing Spatial Filters for Robust EEG Single-Trial Analysis. IEEE Signal Process Mag. 2008;25(1):41–56.

5. Zich C, Debener S, De Vos M, Frerichs S, Maurer S, Kranczioch C. Lateralization patterns of covert but not overt movements change with age: An EEG neurofeedback study. Neuroimage. 2015;116:80–91.

6. Bonnet L, Lotte F, Anatole L. Two Brains , One Game : Design and Evaluation of a Multi-User BCI Video Game Based on Motor Imagery. IEEE Trans Comput Intelligene AI games. 2013;5(2):185–98.

7. Muñoz JE, Ríos LH, Henao OA. Low Cost Implementation of a Motor Imagery Experiment with BCI system and its use in neurorehabilitation. Conference Proceedings IEEE Eng Med Biol Soc. 2014. p. 1230–3.

8. Zich C, De Vos M, Kranczioch C, Debener S. Wireless EEG with individualized channel layout enables efficient motor imagery training. Clin Neurophysiol. International Federation of Clinical Neurophysiology; 2015;126(4):698–710.

9. Fisher R. The use of multiple measurements in taxonomic problems. Ann Eugen. 1936;7(2):179–88.

10. Bell AJ, Sejnowski TJ. An information-maximization approach to blind separation and blind deconvolution. Neural Comput. 1995 Nov;7(6):1129–59.

11. Pfurtscheller G, Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol. 1999 Nov;110(11):1842–57.

12. Rorden C, Brett M. Stereotaxic display of brain lesions. *Behav Neurol* [Internet]. 2000 [cited 2016 Aug 29];12(4):191–200. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11568431>
13. Hua K, Zhang J, Wakana S, Jiang H, Li X, Daniel S, et al. Tract Probability Maps in Stereotaxic Spaces: Analyses of White Matter Anatomy and Tract-Specific Quantification. *Neuroimage*. 2009;39(1):336–47.
14. Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Gollub RL, Hua K, et al. Reproducibility of Quantitative Tractography Methods Applied to Cerebral White Matter. *NeuroIm*. 2008;36(3):630–44.
15. Leemans A, Jeurissen B, Sijbers J, Jones DK. ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data. 17th Annual Meeting of Intl Soc Mag Reson Med. Hawaii, USA; 2009. p. 3537.
16. Tournier J, Mori S, Leemans a. Diffusion Tensor Imaging and Beyond. *Magn Reson ...* [Internet]. 2011;65(6):1532–56. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/mrm.22924/full>
17. Leemans A, Jones DK. The B-matrix must be rotated when correcting for subject motion in DTI data. *Magn Reson Med* [Internet]. 2009 Jun [cited 2016 Aug 29];61(6):1336–49. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19319973>
18. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. *Magn Reson Med* [Internet]. 2000 Oct [cited 2016 Aug 29];44(4):625–32. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11025519>
19. Sea Lee J, Han M-K, Hyun Kim S, Kwon O-K, Hyoung Kim J. Fiber tracking by diffusion tensor imaging in corticospinal tract stroke: Topographical correlation with clinical symptoms. *Neuroimage*. 2005;26(3):771–6.