Neural Reorganization Accompanying Upper Limb Motor Rehabilitation from Stroke with Virtual Reality-Based Gesture Therapy

Article *in* Topics in Stroke Rehabilitation · May 2013

DOI: 10.1310/tsr2003-197 · Source: PubMed

Felipe Orihuela-Espina
Instituto Nacional de Astrofísica, Óptica y Electrónica (INAOE)

Isabel Fernández del Castillo
Universidad Panamericana

Erick Pasaye
Universidad Nacional Autónoma de México

Neural Reorganization Accompanying Upper Limb Motor Rehabilitation from Stroke with Virtual Reality-Based Gesture Therapy

Felipe Orihuela-Espina, PhD,[1] Isabel Fernández del Castillo, MD,[2] Lorena Palafox, MSc,[2] Erick Pasaye, MSc,[3] Israel Sánchez-Villavicencio, MD,[2] Ronald Leder, PhD,[3] Jorge Hernández Franco, MD,[2] and Luis Enrique Sucar, PhD[1]

[1]National Institute of Astrophysics, Optics and Electronics (INAOE), Puebla, Mexico; [2]National Institute of Neurology and Neurosurgery (INNN), Mexico City, Mexico; [3]National Autonomous University of Mexico (UNAM), Mexico City, Mexico

Background: Gesture Therapy is an upper limb virtual reality rehabilitation-based therapy for stroke survivors. It promotes motor rehabilitation by challenging patients with simple computer games representative of daily activities for self-support. This therapy has demonstrated clinical value, but the underlying functional neural reorganization changes associated with this therapy that are responsible for the behavioral improvements are not yet known. **Objective:** We sought to quantify the occurrence of neural reorganization strategies that underlie motor improvements as they occur during the practice of Gesture Therapy and to identify those strategies linked to a better prognosis. **Methods:** Functional magnetic resonance imaging (fMRI) neuroscans were longitudinally collected at 4 time points during Gesture Therapy administration to 8 patients. Behavioral improvements were monitored using the Fugl-Meyer scale and Motricity Index. Activation loci were anatomically labelled and translated to reorganization strategies. Strategies are quantified by counting the number of active clusters in brain regions tied to them. **Results:** All patients demonstrated significant behavioral improvements ($P<.05$). Contralesional activation of the unaffected motor cortex, cerebellar recruitment, and compensatory prefrontal cortex activation were the most prominent strategies evoked. A strong and significant correlation between motor dexterity upon commencing therapy and total recruited activity was found ($r^2=0.80$; $P<.05$), and overall brain activity during therapy was inversely related to normalized behavioral improvements ($r^2=0.64$; $P<.05$). **Conclusions:** Prefrontal cortex and cerebellar activity are the driving forces of the recovery associated with Gesture Therapy. The relation between behavioral and brain changes suggests that those with stronger impairment benefit the most from this paradigm. **Key words**: *functional magnetic resonance imaging, plasticity, rehabilitation, stroke, virtual reality*

Stroke is regarded as the leading cause of motor disability.[1] After a stroke, patients undergo rehabilitation to recover lost motor skills; the goal of rehabilitation is to allow patients to continue their lives and have the best possible quality of life with minimal dependence on others. Motor rehabilitation therapies range from classic occupational therapies to advanced technology-assisted therapies.[2-5] Despite apparent advances, rehabilitation therapy remains an art. In arm function recovery, for example, technology-assisted therapies may not outperform more classic alternatives; similarly, repetitive task training, one of the most frequent types of therapy, has not been demonstrated to be among the most effective.[2] The best time for training to improve outcome is unclear, and current rehabilitation treatments have a disappointingly modest effect on impairment after stroke.[6]

Arguably, the strongest factor guiding functional reorganization following a cerebrovascular event is the location and extent of the lesion. Nevertheless, therapy is still a contributing factor in sheering plasticity.[7] Discharge location can range from home with no therapy to an inpatient rehabilitation facility.[6] In cases where therapy is administered in the chronic stage, naturally occurring brain plasticity is virtually over.[8] Having missed the window of opportunity occurring at acute and subacute stages in which natural brain plasticity peaks, therapy-induced plasticity has only a narrow margin of maneuver.[8] This fact

Top Stroke Rehabil 2013;20(3):197–209

www.strokejournal.com

doi: 10.1310/tsr2003-197

underscores the importance of understanding longitudinal changes in cortical activity as therapy takes place in order to maximize recovery, ensure optimum therapy planning, and improve the prognosis. Researchers have started to delineate some of the most common functional reorganization mechanisms (*when* and *how*) and strategies (*where*) occurring either naturally[9,10] or following specific therapies.[11-13] A stroke lesion may disturb the complex balance of excitatory and inhibitory influences within the motor network. In this sense, a remote effect may occur by which abnormal interactions among regions remote from the lesion might also contribute to motor impairment after stroke.[14]

Virtual reality-based rehabilitation therapies capitalize on computer-generated environments to present the rehabilitation exercises in practical friendly settings.[4,15,16] Proponents of such therapies allege several advantages: low cost, an engaging environment, real-time customizability and wide adaptability to patient requirements and progress, capabilities for recording performance, record keeping and yielding feedback in real-time to both patient and therapist, and the possibility of being used with minimal therapist supervision, thereby facilitating home prescription.

Gesture Therapy (GT) is a recently developed virtual reality–based rehabilitation system.[5,17] The patient is motivated to repeat rehabilitation-focused movements disguised as serious games simulating daily activities. GT is aimed at home usage in low and middle income countries because (a) it costs very little (~$1,000 per unit); (b) it reduces dependency on the families, therapist, and health care systems; and (c) it minimizes the therapist workload. Preliminary clinical evaluation has already demonstrated the clinical benefit of GT.[17] The next step involves pinpointing the mechanisms and strategies underpinning observable behavioral recovery, defined as upper limb motor recovery following GT administration.

Three studies have explored cortical reorganization associated with the IREX (GestureTek Health, Canada) virtual reality–based system therapy administered to patients with stroke[18,19] and cerebral palsy.[20] These studies highlight the reduction of aberrant cortical activation prior to the therapy that diminishes as reorganization shifts activity to the ipsilesional primary sensorimotor cortex. For instance, the case report by You et al[20] found that in a child, contralateral sensorimotor cortex activation replaced bilateral activity in the primary sensorimotor cortex (SM1) and ipsilateral activity in the supplementary motor area present before therapy.

This feasibility study quantified the occurrence of neural reorganization strategies underlying motor improvements as they occurred during the practice of a virtual reality–based therapy such as GT. To that end, we quantified the longitudinal occurrence of known functional reorganization strategies before, during, and after a GT regime in a small cohort as imaged with functional magnetic resonance imaging (fMRI). Activity loci were identified across subjects and times and followed anatomical labelling affiliated to a named reorganization strategy. Large intersubject variations were anticipated despite efforts to recruit a cohort with roughly homogenous lesion characteristics. Moreover, isolation of therapy-induced changes from those taking place naturally was arduous, but we did not expect much spontaneous recovery in the chronic stage. Notwithstanding these challenges, the dynamic histogram of strategies revealed the interplay of these strategies as the GT occurs. Consistent with literature reports,[8,21,22] we hypothesized that overall cortical activity should decrease as the therapy progressed as a consequence of the progressive abandon of compensatory activity. We further expected GT-evoked reorganization to be strongly linked to strategies that have previously been linked to a good prognosis, such as recruitment of the ipsilesional motor area or high cerebellar activity. We hope the findings of this first snapshot of the GT patients' brain behavior will contribute to the general understanding of recovery following stroke, better illustrate the possibilities of virtual reality–based rehabilitation therapies, and further advance the design of GT.

Methods

Subjects

Individuals with hemiparetic upper limb impairment caused by stroke at least 6 months (chronic stage) prior to the beginning of the study were candidates for inclusion. Eight patients (4 males and 4 females) were recruited from the National Institute of Neurology and Neurosurgery (Mexico City). They were all right handed. For 6 patients, the right upper limb was affected, and for the other 2 (subjects 5 and 7), the left upper limb (nondominant) was affected. The presence of severe pain during movement or articulation instability (shoulder, elbow, or wrist), severe medical problems such as congestive heart failure or convulsive seizures preventing adequate attention to task, and aphasia and apraxia were considered to be exclusion criteria. Clinical assessment of their ictus was found to be hemorrhagic in all cases and located subcortically in all but one patient (subject 3). Subjects signed a consent form before volunteering for the study. Cohort characteristics, clinical evaluation of the lesion extent, medical history, and concomitant medication are summarized in **Table 1**.

The present experiment was part of a larger experiment including 28 patients randomized in 3 groups: 10 control under occupational therapy, 10 intervention under GT without fMRI, and 8 intervention under GT with fMRI. This article presents only the results from the fMRI analysis of the third group (8 patients). Because our aim was to assess therapy-induced plastic changes, no control group was set with respect to fMRI neuroscans.

Gesture Therapy

With GT,[5,17] patients recover function by repeating fundamental movements, and they are enticed to perform these movements by means of games rendering everyday tasks in a virtual reality environment. Games are controlled by means of a gripper incorporating a sphere for tracking and a pressure sensor for grip as illustrated in **Figure 1**. For patients lacking the necessary grip force, a special harness that can be affixed to the forearm is available to provide extra support and ensure that the gripper is always handled properly (GT provides no support for shoulder or elbow). A machine vision system tracks the gripper location to determine arm movements, and the pressure sensor permits finger exercising. If necessary, the vision system can further track the patient's body position to provide a cue about trunk compensation. In this study, we used an early version of GT. Since our study was completed, GT has evolved to include the capability to adapt to the patient's need and progress in real time.[23]

Experiment design

All patients in this cohort were treated with the virtual reality–based GT, which consisted of 20 sessions of 45 minutes each (mean treatment duration ± SD, 39.1 days ± 3.1 days), under a therapist's supervision. The game set used for this study is that of the Armeo system (Hocoma, Switzerland). The subset of games practiced during the experiment included rain mug, reveal picture, fruit shopping, and egg cracking. These games focused on horizontal abduction/adduction and elevation/depression movements; the latter 2 require gripping. During the sessions, the games were randomly varied in order by the therapists in periods of 3 minutes. Feedback was given to the patients regarding time remaining and percentage of task achieved. The games had different levels of challenge, but difficulty remained constant during a game.

Patients' motor skills were assessed before the first GT session and again after the final session at the end of the therapy by means of validated scales (Fugl-Meyer scale[24] and Motricity Index[25]). Brain scans were carried out before and after the therapy, as well as at 2 other intermediate time points after the 7th and 14th rehabilitation sessions, respectively (mean time between MRI scans ± SD, 13.9 ± 1.9 days), to capture longitudinal variations in cortical activity. At each neuroimaging session, both structural (T1-weighted spoiled gradient echo [SPGR]) and functional (echo planar imaging blood oxygen level dependent [EPI-BOLD]) sequences of magnetic resonance neuroimages (General Electric Healthcare HDXT 3.0T, Milwaukee, WI) were acquired. The anatomical scan collected 180 slices sized 256 x 256 with isotropic 1 x 1 x 1 mm voxel size. The functional scans (30 slices sized 64 x 64 with 3.75 x 3.75 x 5 mm voxel size) followed a classical block stimulus train alternating 6 blocks of 20 seconds rest and 20 seconds task. In total, 120 functional volumes (TR = 2 s; TE = 40 ms; field of view [FOV] = 24 cm) were acquired during each MRI scan. During the

Table 1. Cohort characteristics, clinical evaluation of the lesion extent, medical history, and concomitant medication

						Location and extent of lesion at session 1							
Subject	Age, years	Gender	Handedness	Affected upper limb	Time from last stroke at therapy onset, months	Multiple strokes	Cortical / subcortical	H	Origin	Brain regions affected by lesion	Other affected functions	Medical history	Concomitant medication
1	24	F	R	R	29	No	S	H	L internal carotid artery	Supratentorial and extra-axial	R pyramidal syndrome	Not specified	None
2	35	M	R	R	9	No	S	H	Middle cerebral artery	Internal capsule	No	Hypertension	Captopril
3	49	M	R	R	21	No	C	H	L middle cerebral artery	Basal ganglia	No	Not specified	None
4	24	M	R	R	66	No	S	H	Posterior cerebral artery and left anterior cerebral artery	R temporal-occipital region	No	Epilepsy, dislipidemy, obesity	Enalpril, amiodarona, metoprolol, aldactone
5	55	F	R	L	28	No	S	H	Subarachnoid	Thalamus and posterior limb of the right internal capsule	Pyramidal and sensitive syndromes	Hypertension	Homeopathic antihypertensive agent
6	30	M	R	R	127	No	S	H	Anterior cerebral artery	L parietal-temporal	R pyramidal syndrome	Dislipidemy	None
7		F	R	L	78	No	S	H	R posterior communicant artery	L sylvian valley	No	Not specified	None
8	54	F	R	R	10	Yes	S	H	Basilar artery	Mesencephalon and pons varolii	No	Stroke	Captopril

Note: H = hemorrhagic; L = left; R = right. M = male; F = female;

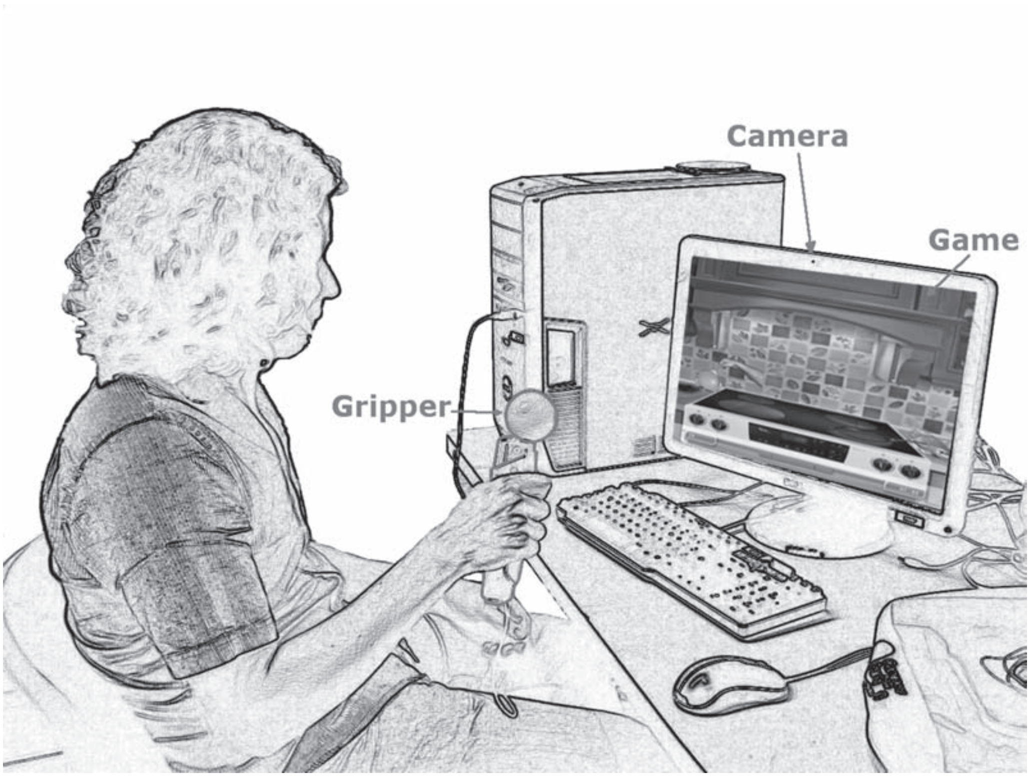


Figure 1. The Gesture Therapy (GT) platform. The patient plays a significant (ie, representative of an everyday task) virtual reality game that forces repetitive movements. To interact with the game, the patient holds a gripper incorporating a ball (top) and a pressure sensor (handle). The gripper's ball is tracked and the movements are communicated to the GT platform. The sensor further allows finger exercising. Like other virtual reality rehabilitation platforms, GT camouflages the rehabilitatory exercises as a gaming experience; however, it differs in its intensive use of decision-theoretic techniques for guiding the therapy.

task, the patients were shown a video of a GT game and were asked to imagine playing the game while holding a phantom control gripper. The real gripper contains ferromagnetic elements. Their movement was constrained by tying their arms and head. Outcome measures included behavioral performance and brain behavior.

Behavioral metrics

Motor skills were assessed using Fugl-Meyer scale[24] and Motricity Index.[25] Partial changes in the different subcriteria and overall changes in the scores before and after therapy were assessed using nonparametric Mann-Whitney *U* test at an $\alpha = 5\%$ significance level (R statistical package 2.12.1).

Image processing and analysis

All neuroimage processing and analysis was carried out using the Statistical Parametric Mapping tool SPM8.[26] MRI scans were realigned to correct for motion, coregistered to overlay structural and functional scans, normalized to a standard template, and finally smoothed using a Gaussian filter (8 pixels wide). Thirty-two statistical parametric maps (8 subjects x 4 MRI scans) thresholded at $P < .001$ significance level were obtained. The maps were qualitatively assessed by one of the researchers (F.O.E.). Active pixels were counted to compute longitudinal variations in overall active volume and changes were assessed using Friedman test at $P < .05$.

Quantification of functional reorganization strategies

Reorganization strategies capture activity shifts in the brain. **Table 2** summarizes known functional reorganization strategies following stroke.[8,21,22,27] Active loci were labelled with brain regions using the automatic anatomical labelling (AAL) SPM toolbox[28] and the cluster labelling procedure. After parcellation with AAL, active clusters were grouped according to the anatomical location. This was assessed quantitatively in terms of the reorganization strategy associated with the location. Counting the active clusters per regions of the different strategies provides a quantitative measure of the use of the reorganization strategy. Further details of the setup, including incidences during data acquisition, the design matrix, and additional analyses carried out, are provided in the technical report.[29]

Results

Behavioral outcome

Individual improvements according to both the Fugl-Meyer scale and Motricity Index were observed in all participants. **Figure 2** summarizes the behavioral outcomes. Overall significant improvements in motor skills were observed on both scales (Mann-Whitney *U* test; $P<.05$). In addition, the Fugl-Meyer scale further revealed statistically significant improvements in all criteria, that is shoulder/elbow/forearm, hand, wrist, and coordination. Motricity Index confirmed statistically significant improvements in hand grip, but improvements in elbow flexion and shoulder abduction did not reach statistical significance. In summary, behavioral improvement was demonstrated at both the patient and cohort levels, and this was confirmed for all elements of upper limb rehabilitation. In particular, improvements were mostly manifested as a greater amplitude/range of movement. Favored by this greater amplitude, individuals were capable of other activities such as combing their hair and brushing their teeth with minimal help and in specific cases even without help from a third person.

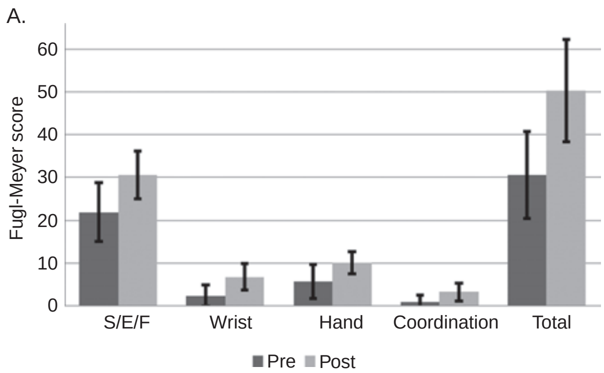
Analysis of brain activity

Figure 3 illustrates qualitative findings established for 2 exemplary subjects. Some of the

Table 2. Common functional reorganization strategies following stroke affecting the motor cortex

Reorganization strategy	Functional interpretation
Ipsilesional activation of M1[21,22]	Activation shifts toward infarct rim (perilesional activation) or posterior and occasionally inferior extension. The shift may represent neural unmasking or disinhibition of existing latent connections or recruitment of new neurons not normally devoted to motor functions (vicariance) and establishment of new synapsis.
Contralesional activation of the M1[22,32]	The unaffected contralesional primary motor cortex undertakes the duties of its damaged counterpart. Often regarded as less efficient than ipsilesional activation, it may indicate an unconscious lack of effort.
Bilateral recruiting of secondary motor areas (SMA, PM)[21,33-35]	PM becomes overactivated at a late stage of recovery, indicating a redistribution of workload. It may reflect recruitment of pre-existing large-scale distributed motor network rather than genuine reorganization. Even simple tasks become complex for patients. Thus, it may reflect an increase in executive control. (SMA and PM are associated with executing complex tasks.)
Recruitment of nonmotor areas (PFC, PPC, ACC, and insula)[21,33,35,36]	May reflect cortical compensatory cognitive strategies. Lesser attenuation with time suggests recourse to normal behavior; compensatory strategies become less necessary as recovery progresses.
Recruitment of the cerebellum[27]	Cerebellar activation may be a consequence of its role in motor learning or haemodynamic alterations such as diaschisis. Change in cerebellar activity ipsilateral to the paretic side is associated with good prognosis. Activation of cerebellum ipsilateral to injury increases transiently after stroke regardless of the recovery.
Recruitment of the basal ganglia[33]	Cerebellar activation may originate in subcortical structures such as thalamus and basal ganglia; the latter is involved in motor skill learning. fMRI is not well suited for the study of the basal ganglia, and thus this strategy is not further considered in this study.
Swerving of the CST[10]	Damage of the brainstem could block propagation of motor signal. If damaged, the new tract may join the pons further down. We focus on lesions on the primary motor cortex and thus do not consider this strategy here.

Note: ACC = anterior cingulate cortex; CST = cortico-spinal tract; fMRI = functional magnetic resonance imaging; M1 = primary motor cortex; PFC = (dorsolateral) prefrontal cortex; PM = premotor cortex; PPC = posterior parietal cortex; SMA = supplementary motor area.



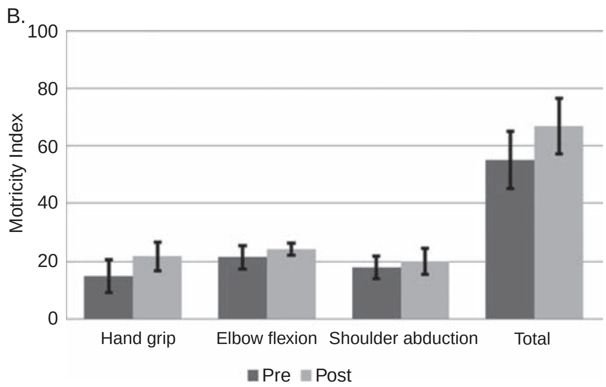


Figure 2. Cohort mean motor skills performance prior to (in dark gray) and after the therapy (in light gray). (A) Fugl-Meyer scale; the first bar gives shoulder/elbow/forearm (S/E/F) scores. (B) Motricity Index. Individual scoring criteria and total scores are shown in both cases. Behavioral improvements can be appreciated in both scales in all criteria. All differences were statistically significant ($P<.05$) except for the Motricity Index elbow flexion and shoulder abduction. Error bars correspond to 1 SD.

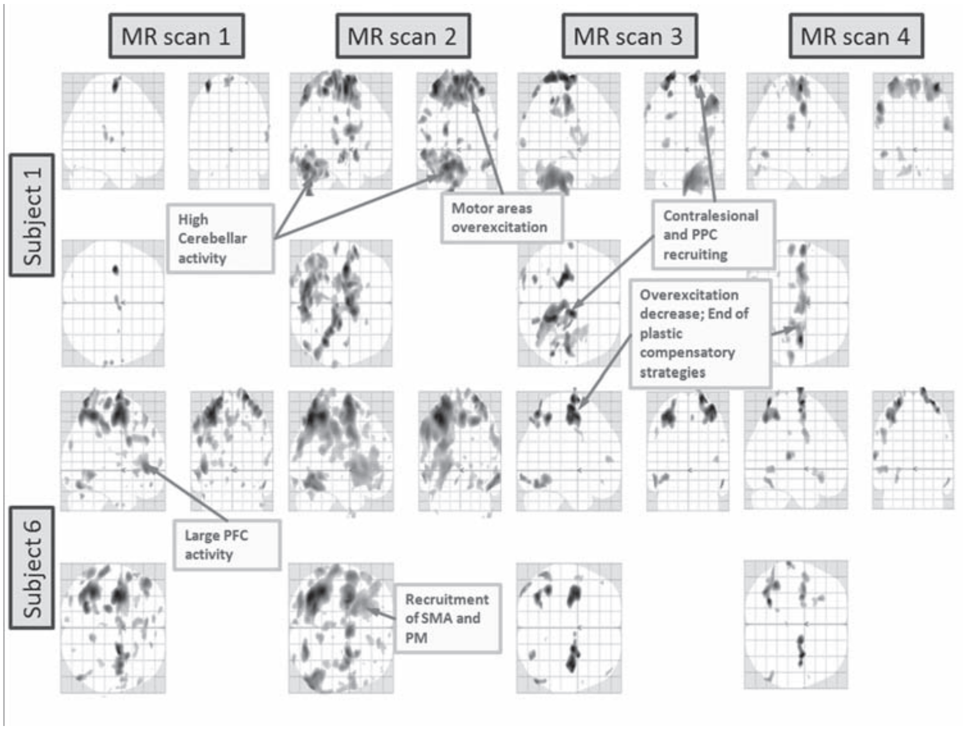


Figure 3. Statistical parametric mappings for exemplary subjects 1 (top row) and 6 (bottom row) across the 4 MRI scans ($P<.001$). The scans on the left were taken prior to the start of therapy; those on the right were taken after the end of the planned therapy. MRI scans 2 and 3 correspond to intermediate therapy sessions (7th and 14th, respectively). The maps are illustrated in the usual glass brain in all 3 planes (sagittal, coronal, and axial). Some of the reorganization strategies are highlighted. Therapy duration averages 39 days with MRI scans separated by 14 days on average. Changes for the cohort have been detailed in the preceding report.[29] PPC = posterior parietal cortex; PFC = prefrontal cortex; PM = premotor cortex; SMA = supplementary motor area.

reorganization strategies in **Table 2** can be easily observed. The active pixels were counted and the overall longitudinal changes in the active volume were quantified. Although changes in active volume were progressive with no step reaching statistical significance (Friedman test, $P = .3784$), a peak in activity in the second session was observed. Lower initial activity has been hypothesized to originate from a lack of task engagement when the subject is in total task naïvity and is unable to develop a task execution strategy.[30] In addition, trivial counting of found active clusters suggested a need to recruit cortical regions in subjects 5 and 7, whose affected limb was the nondominant one.

Time from stroke was found to be an explanatory variable to determine the unleashing of certain strategies such as the activation of the ipsilesional motor cortex and the recruitment of the prefrontal cortex and anterior cingulate cortex ($P < .05$). Also, the recruitment of insula may be dependent on the handedness ($P < .05$). As expected, activation of the ipsilesional motor cortex was linked to a good behavioral improvement as indicated by changes in 3 of the 4 Fugl-Meyer scale elements (shoulder/elbow/forearm, hand, and coordination; $P < .05$). Similarly, changes in elbow flexion and total improvements according to the Motricity Index were found to be predictors of activity in the prefrontal cortex ($P < .05$).

The histogram of the functional reorganization strategies is quantified in **Table 3**. In general terms, GT appears to accentuate contralesional activation of the unaffected SM1. This may be unfortunate, because contralesional activation has been suggested to be linked to poorer prognosis than ipsilesional activation. Recruitment of the anterior cingulate cortex and insula appeared to be rare in this group, but cerebellar recruitment was high. An overall abandon of compensatory strategies was also manifested. In addition, every subject's brain underwent different reorganization partly because of the different lesion location and extent. The large modification of recruitment patterns, proxy of massive reorganization, and extensive activation proxy of therapy-induced hyperexcitability are characteristics of the changes in the sensorimotor cortex of recovered stroke patients.[7,11]

The study established a weak relationship between improvements as captured by increments in the Fugl-Meyer index score and the continuous recruitment of not fully destroyed ipsilesional motor area for 3 individual scores: shoulder/elbow/forearm ($r^2 = 0.17$; $P < .05$), hand ($r^2 = 0.18$; $P < .05$), and coordination ($r^2 = 0.24$; $P < .05$). Also, as shown in **Figure 4**, a strong significant correlation can be established between the motor dexterity upon starting the therapy and the total amount of activity across MRI scans, as represented by the number of active clusters involved in rehabilitation strategies. Focusing on subcortical stroke, that is excluding subject 3, those subjects arriving at therapy with greater disability only experienced limited plastic changes over the course of the therapy ($r^2 = 0.80$; $P < .05$), perhaps reflecting the lower room for reorganization of a more extensively damaged brain. Yet, this limited reorganization affords the largest improvements in motor recovery once normalized by status upon beginning therapy ($r^2 = 0.64$; $P < .05$). This may indicate that in subcortical stroke, the activity induced by the GT has greater effect for more severe disability, which perhaps reflects that any reorganization, even if limited, results in meaningful behavioral improvements when the damage is so devastating in terms of motor disability. Moreover, the above observation of subjects 5 and 7 (nondominant limb affected) demanding more activity can now be contextualized, because they started therapy with milder functional disability.

Discussion

The functional reorganization occurring in a small cohort of patients surviving a cerebrovascular event undergoing so-called Gesture Therapy has been characterized. The picture has been complemented with the patients' clinical history, medication, and clinical evaluation in terms of motor skills evoked by the therapy. The behavioral outcomes observed in this study add to the evidence of the clinical benefit of GT.[17] This, together with the preceding technical report,[29] is the first picture of the longitudinal plastic changes of patients in GT. Also, it is perhaps the most complete picture so far of the reorganization following any virtual reality–based motor rehabilitation. Previous reports lack in-between data and were constrained to specific regions of interest.[18-20] In contrast with these

Table 3. Histogram of functional reorganization strategies

Subject (affected limb)	Session	Ipsilesional activation	Contralesional activation of unaffected SM1	Recruitment of bilateral SMA and PM (L/R)	Recruitment of nonmotor areas				Recruitment of the cerebellum (inc. vermis)	Others	
					PFC	PPC	ACC (L/R)	Insula (L/R)		Subcortical (L/R)	Limbic exc. ACC (L/R)
1 (R)	1	1	1	(1/1)	3	0	(0/0)	(0/0)	3	(0/0)	(0/0)
	2	2	4	(1/1)	5	5	(0/1)	(0/2)	18	(2/4)	(1/3)
	3	3	3	(1/0)	3	7	(0/0)	(2/0)	14	(2/0)	(4/0)
	4	2	4	(2/1)	7	6	(0/0)	(0/0)	12	(0/0)	(0/0)
2 (R)	1	3	3	(0/1)	7	10	(0/0)	(0/0)	2	(0/0)	(0/0)
	2	1	4	(1/2)	16	4	(0/0)	(0/1)	1	(0/0)	(0/0)
	3	0	2	(0/0)	5	6	(0/0)	(0/0)	1	(0/0)	(0/0)
	4	1	0	(0/0)	11	4	(0/0)	(0/0)	1	(0/0)	(0/0)
3 (R)	1	1	3	(4/2)	8	5	(0/0)	(0/0)	0	(0/0)	(0/0)
	2	1	3	(2/1)	3	2	(0/0)	(0/0)	0	(0/0)	(0/0)
	3	3	0	(1/0)	3	1	(0/0)	(0/0)	1	(0/0)	(0/0)
	4	1	2	(0/0)	1	2	(0/0)	(0/0)	0	(0/0)	(0/0)
4 (R)	1	3	0	(1/1)	7	3	(0/0)	(0/0)	11	(0/0)	(0/0)
	2	3	0	(1/1)	7	3	(0/0)	(0/0)	11	(0/0)	(0/0)
	3	2	1	(1/3)	14	5	(0/1)	(0/0)	15	(0/0)	(1/3)
	4	1	5	(1/1)	45	11	(0/1)	(1/2)	23	(6/5)	(5/4)
5 (L)	1	2	4	(1/2)	15	10	(0/0)	(0/0)	1	(0/0)	(0/0)
	2	2	3	(4/6)	21	5	(0/0)	(0/0)	13	(0/0)	(0/1)
	3	2	2	(1/1)	21	6	(0/0)	(2/3)	23	(3/1)	(0/1)
	4	1	3	(1/3)	15	9	(0/0)	(0/1)	13	(0/1)	(0/3)
6 (R)	1	4	3	(2/2)	33	5	(1/1)	(0/2)	3	(1/3)	(2/1)
	2	2	1	(2/4)	42	7	(0/1)	(0/1)	4	(2/4)	(1/2)
	3	2	2	(2/0)	7	6	(0/0)	(0/0)	0	(0/0)	(0/0)
	4	2	2	(1/0)	7	3	(0/0)	(0/1)	0	(0/1)	(0/0)
7 (L)	1	2	3	(1/1)	14	5	(0/0)	(1/0)	3	(0/0)	(0/0)
	2	1	2	(2/2)	29	10	(0/0)	(1/1)	7	(5/2)	(3/2)
	3	1	2	(1/1)	22	5	(0/0)	(1/2)	14	(2/2)	(1/4)
	4	1	1	(1/1)	42	6	(3/1)	(1/3)	14	(7/8)	(4/4)
8 (R)	1	0	0	(0/0)	0	0	(0/0)	(0/0)	0	(0/0)	(0/0)
	2	2	3	(1/3)	16	5	(1/0)	(0/0)	20	(1/0)	(1/2)
	3	1	1	(1/1)	36	7	(1/1)	(1/1)	20	(9/7)	(4/4)
	4	1	4	(3/1)	26	8	(1/0)	(1/0)	12	(1/0)	(3/2)

Note. Values indicate the number of statistically significant clusters found on the corresponding regions. Pairs of numbers denote the left (L) and right (R) hemispheres. ACC = anterior cingulate cortex; exc. = excluding; inc. = including; PFC = prefrontal cortex; PM = premotor cortex; PPC = posterior parietal cortex; SM1 = primary sensorimotor cortex; SMA = superior motor area.

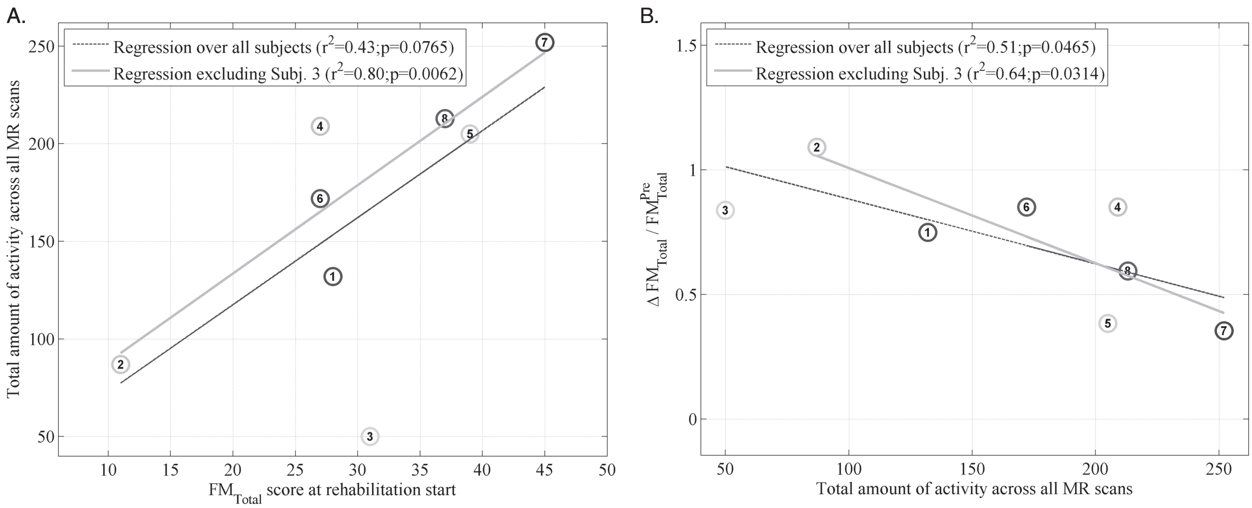


Figure 4. Relations between overall brain activity and Fugl-Meyer scale (FM) scores. (A) Total amount of activity across magnetic resonance (MR) scans represented by the number of active clusters involved in rehabilitation strategies as explained by the motor dexterity upon starting the therapy. (B) Normalized improvements in motor dexterity upon completion of the therapy explained by the total amount of activity across MR scans represented by the number of active clusters involved in rehabilitation strategies. Subject numbers are labelled appropriately. Regressions for the whole cohort (thin dashed line) and the subcohort with subcortical ictus only (thick line; excluding subject 3) are shown. Patients with milder impairment benefit less from this paradigm.

studies, we did not necessarily find ipsilesional SM1 activation following the virtual reality therapy; instead, we found a very diverse pattern of reorganization. Differences in the approach to the analysis and ultimately the different therapy may be responsible for the disparity.

Our results suggest that GT in its current form may not sufficiently stimulate ipsilesional activity, often associated with better prognosis. This is not necessarily disheartening as the well-established constraint-induced movement therapy also keeps smaller cortical representation on the affected side than on the healthy side.[12] In contrast, large recruitment of the cerebellum, associated with good prognosis,[27] is present in a large part of our cohort. Although each damaged brain proceeds with its own reorganization strategy, there is a common tendency to drop compensatory strategies as the therapy progresses, decreasing overall activity as hypothesized. This pattern has been identified in recovery from stroke,[21] suggesting that this effect may be independent of the therapy. The GT exercise has hinted at a weak relation between improvements as captured by the Fugl-Meyer score and the continuous recruitment of ipsilesional motor areas that are not fully destroyed. This is consistent with the general perception that this strategy is associated with good prognosis.

After normalizing the absolute progression on the dexterity scores by the score at therapy onset, we observed that those patients who arrive at therapy with milder impairment exhibit lower improvements, despite recruiting higher overall brain activity. In other words, those with more severe impairment for which the brain can only afford limited reorganization benefit the most from this therapy. This finding is consistent with previous studies[18,20] of functional reorganization following motor impairment treated with a virtual reality–based therapy, as illustrated in **Figure 5**.

Arguably, the most important limitation of this study is the intrinsic group heterogeneity. It is extremely difficult to homogenize the cohort because brain infarcts always present individual characteristics, thus limiting the amount of group inference that can be made. Moreover, age variability, which can affect speed and strength of plastic changes, has been ignored here. In

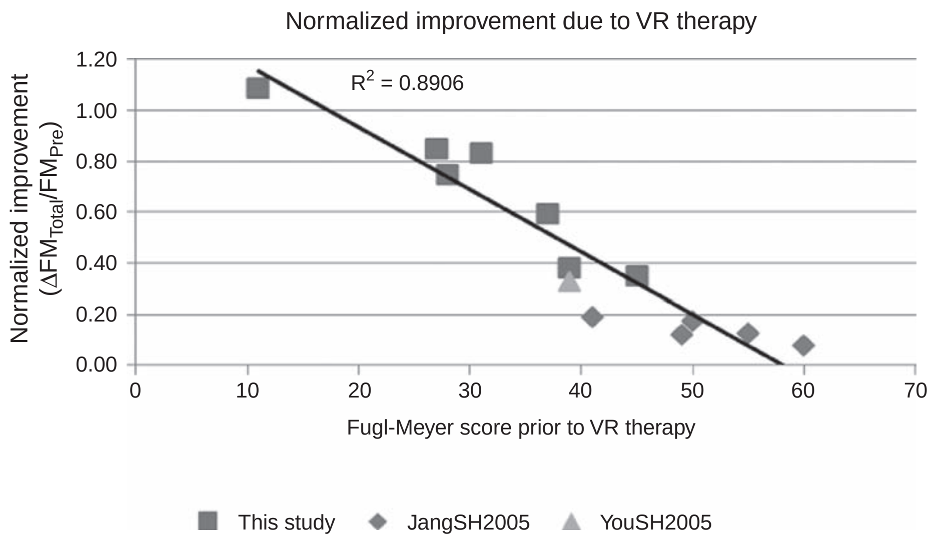


Figure 5. Normalized improvement after virtual reality (VR) therapy. The VR paradigm appears to benefit most patients, with greater initial impairment at the start of the therapy. The scatterplot shows normalized motor improvement and motor dexterity upon arrival at therapy. Data are from the present study and 2 others,[18,20] one of which[20] is a case study of a single subject. The relation follows a linear trend ($r = .89$).

addition, the present analysis suffers from an inherent limitation when lesioned brains are normalized to a template. The lack of a control group is partially justified when the goal is neither to evaluate the clinical effects of the therapy nor to compare against other physiotherapeutic approaches, but to assess therapy-induced plastic changes.[7,12] Yet, its absence means that we can only speculate about therapy-induced effects and naturally occurring effects. Nevertheless, naturally occurring recovery is almost certain to occur in the subacute stage rather than the chronic stage. Since the patients in this study are already in the chronic stage, it is likely that the results presented here are mainly a consequence of the therapy and not spontaneous.

Conclusions/Implications

In this study, we aimed to observe and quantify functional reorganization changes associated with virtual reality–based GT. The take-home message is that the clinical benefit of GT is the result of a complex interplay of a number of cortical and subcortical reorganization strategies, of which prefrontal cortex and cerebellum activity are the 2 most prominent. Our results have corroborated the finding reported in the literature that compensatory strategies are dropped as recovery progresses. Finally, we have established a correlation between brain changes and observed behavioral changes. This study has confirmed previous evidence about the clinical benefit of GT in terms of observable behavioral improvements.[5]

We have established the longitudinal changes in the location and intensity of activity resulting from the reorganization strategies evoked by GT. However, we have not yet elucidated how the compensatory plasticity establishes new cortical networks. New networks are likely to exhibit different efficiencies. Measures such as the cognitive burden[31] can shed light on the cortical network efficiency. Another question, still open, is how different strategies combine to recover function. Since the time at which the data reported in this article were collected, a newer GT platform including real-time adaptability of the therapy to the patient's progress has become available.[23] This is likely to have consequences at the cortical level.

Virtual reality–based rehabilitation therapies like GT are perhaps the latest contribution to the growing body of efficacious and potent therapies available to therapists and patients with motor impairments. Virtual reality–based therapies are still young, and the promising behavioral improvements demonstrated in clinical trials must now be paired with the understanding of the underlying cortical and subcortical changes that form the biological basis for recovery. Further studies are needed in this area.

Acknowledgments

Funding support: This work has been funded by Project SALUD-2007-C01-70074 from the Consejo Nacional de Ciencia y Tecnología (CONACYT), the Secretaria de Salud of the Mexican Government, Project 95185 from the FONCICYT (European Union-Mexico), and the Project SEMILLA from the Red Temática de Tecnologías de la Información y Comunicación of CONACYT.

REFERENCES

1. Lloyd-Jones D, Adams RJ, Brown TM, et al (on behalf of the American Heart Association Statistics Committee Wylie-Rossett, and Stroke Statistics Subcommittee). Heart disease and stroke statistics - 2010 update. A report from the American Heart Association. *Circulation.* 2010;121:e46-e215.
2. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. *Lancet Neurol.* 2009;8:741-754.
3. Lo AC, Guarino PD, Richards LG, et al. Robot-assisted therapy for long term upper-limb impairment after stroke. *N Engl J Med.* 2010;362(19):1772-1783.
4. August K, Bleichenbacher D, Adamovich S. Virtual reality physical therapy: a telerehabilitation tool for hand and finger movement exercise monitoring and motor skills analysis. In: *Bioengineering Conference, 2005. Proceedings of the IEEE 31st Annual Northeast*; April 2-3, 2005; pp. 73-74. doi: 10.1109/NEBC.2005.1431931
5. Sucar LE, Luis R, Leder R, Hernández J, Sánchez I. Gesture therapy: a vision-based system for upper extremity stroke rehabilitation. In: *32nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS)*; August 31-September 4, 2010; pp. 3690-3693.
6. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: What can be learned from animal models? *Neurorehabil Neural Repair.* 2012;26(9):923-931.
7. Liepert J, Bauder H, Miltner WHR, Taub E, Weiller C. Treatment-induced cortical reorganization after stroke in humans. *Stroke.* 2000;31:1210-1216.
8. Chen R, Cohen LG, Hallet M. Nervous system reorganization following injury. *Neuroscience.* 2002;111(4):761-773.
9. Jang SH, Ahn SH, Lee J, Cho YW, Son MS. Cortical reorganization of sensori-motor function in a patient with cortical infarct. *NeuroRehabilitation.* 2010;26:163-166.
10. Jang SH, Hong JH, Ahn SH, Son MS, Cho YW. Motor function reorganization in a patient with brainstem lesion: DTT, fMRI and TMS study. *NeuroRehabilitation.* 2010;26:167-171.
11. Liepert J, Miltner WHR, Bauder H, et al. Motor cortex plasticity during constraint-induced movement therapy in stroke patients. *Neurosci Lett.* 1998;250:5-8.
12. Liepert J, Uhde I, Gräf S, Leidner O, Weiller C. Motor cortex plasticity during force-use therapy in stroke patients: a preliminary study. *J Neurol.* 2001;248:315-321.
13. Altenmüller E, Marco-Pallares J, Münte TF, Schneider S. Neural reorganization underlies improvement in stroke-induced motor dysfunction by music-supported therapy. *Ann N Y Acad Sci.* 2009;1169:395-405.
14. Grefkes C, Fink GR. Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches. *Brain.* 2011;134:1264-1276.
15. Holden MK. Virtual environments for motor rehabilitation: review. *CyberPsychol Behav.* 2005;8(3):187-211.
16. Adamovich SV, Fluet GG, Tunik E, Merians AS. Sensorimotor training in virtual reality: a review. *NeuroRehabil.* 2009;25(1):29.
17. Sucar LE, Molina A, Leder R, Hernández J, Sánchez I. Gesture therapy: a clinical evaluation. In: *3rd International Conference of the Institute for Computer Sciences, Social-Informatics and Telecommunications Engineering (ICST) on Pervasive Computing Technologies for Healthcare (Pervasive Health 2009).* 2009:1–5. doi: 10.410B/ICST.PERVASIVEHEALTH2009.6090
18. Jang SH, You SH, Hallet M, et al. Cortical reorganization and associated functional motor recovery after virtual reality in patients with chronic stroke: an experimenter-blind preliminary study. *Arch Phys Med Rehabil.* 2005;86:2218-2223.
19. You SH, Jang SH, Kim YH, et al. Virtual reality-induced cortical reorganization and associated locomotor recovery in chronic stroke: an experimenter-blind randomized study. *Stroke.* 2005;36:1166-1171.
20. You SH, Jang SH, Kim YH, Kwon YH, Barrow I, Hallet M. Cortical reorganization induced by virtual reality therapy in a child with hemiparetic cerebral palsy. *Develop Med Child Neurol.* 2005;47:628-635.

21. Calautti C, Baron JC. Functional neuroimaging studies of motor recovery after stroke in adults. *Stroke.* 2003;34:1553-1566.
22. Buma FE, Linderman E, Ramsey NF, Kwakkel G. Functional neuroimaging studies of early upper limb recovery after stroke: a systematic review of the literature. *Neurorehabil Neural Repair.* 2010;24(7):589-608.
23. Avilés H, Luis R, Oropeza J, et al. Gesture therapy 2.0: adapting the rehabilitation therapy to the patient progress. In: Hommerson A, Lucas P, eds., *Workshop on Probabilistic Problem Solving in Biomedicine in 13th Conference on Artificial Intelligence in Medicine (AIME'11).* Bled, Slovenia; 2011: pp. 3-14. http://probiomed.cs.ru.nl/papers/aviles.pdf
24. 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.* 1975;7(1):13-31.
25. Demeurisse G, Demol O, Robaye E. Motor evaluation in vascular hemiplegia. *Eur Neurol.* 1980;19:382-389.
26. Statistical parametric mapping. http://www.fil.ion.ucl.ac.uk/spm/. Accessed February 25, 2013.
27. Small SL, Hlustik P, Noll DC, Genovese C, Solodkin A. Cerebellar hemispheric activation ipsilateral to the paretic hand correlates with functional recovery after stroke. *Brain.* 2002;125:1544-1557.
28. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labelling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage.* 2002;15:273-289.
29. Orihuela-Espina F, Sucar LE. Functional reorganization strategies associated to motor rehabilitation gesture therapy. Technical Report CCC-11-001. Coordinación de Ciencias Computacionales. Instituto Nacional de Astrofísica, Óptica y Electrónica (INAOE); June 2011.
30. Leff DR, James DRC, Orihuela-Espina F, Yang GZ, Darzi AW. The frontal cortex is activated during learning of endoscopic procedures (Ohuchida et al., Surgical Endoscopy, January 2009) [letter]. *Surg Endosc.* 2010;24:968-969.
31. James DRC, Orihuela-Espina F, Leff DR, et al. Cognitive burden estimation for visuomotor learning with fNIRS. In: *Medical Image Computing and Computer-Assisted Intervention (MICCAI 2010) in Lecture Notes in Computer Science.* 2010;6363:319-326. http://link.springer.com/chapter/10.1007%2F978-3-642-15711-0_40.
32. Feydy A, Carlier R, Roby-Brami A, et al. Longitudinal study of motor recovery after stroke: recruitment and focusing of brain activation. *Stroke.* 2002;33:1610-1617.
33. Calautti C, Leroy F, Guincestre JY, Baron JC. Dynamics of motor network overactivation after stratiocapsular stroke: a longitudinal pet study using a fixed-performance paradigm. *Stroke.* 2001;32:2534-2542.
34. Ward NS, Newton JM, Swayne OBC, et al. Motor system activation after subcortical stroke depends on corticospinal system integrity. *Brain.* 2006;129:809-819.
35. Nelles G, Spiekermann G, Jueptner M, et al. Evolution of functional reorganization in hemiplegic stroke: a serial positron emission tomographic activation study. *Ann Neurol.* 1999;46:901-909.
36. Nelles G, Jentzen W, Bockish A, Diener HC. Neural substrates of good and poor recovery after hemiplegic stroke: a serial PET study. *J Neurol.* 2011;258:2168-2175.