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rTMS and CIMT for Neurofunctional Recovery in Chronic Stroke

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Abstract

Background: The purpose of the study was to investigate the effect of high frequency rTMS with constraint induced movement therapy (CIMT) on Upper extremity motor function. Clinical Stroke Assessment Scales and fMRI was used to assess the response of CIMT with rTMS on blood oxygenation-level dependent (BOLD) sequence component.

Methodology: RCT was conducted at All India Institute of Medical Sciences, New Delhi, on chronic stroke patients (N=60) between 12 to 36 months of index event with atleast 10° of wrist extension, 10° of thumb abduction, Brunnstorm stage 2-4; NIHSS 4–20. Patients were randomized to CIMT alone (Group A n=30) & rTMS with CIMT (Group B n=30). rTMS (10 Hz, 750 pulses with 110%RMT) was administered for 3 weeks (5days/week). Radiological Assessment of the patients was done with fMRI (BOLD) along with assessment of Fugl Meyer (FM), Barthel Index, and modified Rankin Scales (MRS) at baseline, 3 weeks (Post intervention) & 3 month (follow up)

Results: FM showed statistically significant improvement in group B as compared to group A at 3 weeks (95%CI: -12.4 to -9.3, p=0.003) and 3months (95%CI: 7.4 to 4.2, p=0.01). Repeated measure ANOVA showed that the mean groups were different at all-time points indicating some degree of improvement in all the subjects (F=3.4, p=0.01; F=5.4, p=0.002). The BOLD cluster activation was compared between two groups; there was increase in the number of clusters found in Group B.

Conclusion: Both the groups showed improvement, increased cluster count showing alterations in cortical activations (fMRI-BOLD) after CIMT with rTMS in patients with chronic stroke indicated more degree of clinical improvement in upper extremity function.

Keywords: Cortical reorganization • fMRI-BOLD • High Frequency rTMS • Cluster activation

Introduction

Stroke is the most common non communicable disease which leads to serious disability [1]. One of the common deficits following stroke is upper limb motor impairment & motor control dysfunction which can significantly impact on activities of daily living and performance [2]. Variability in the nature and extent of the upper limb is well accepted & reported [3].

A large number of upper limbs neuromotor approaches are currently available but CIMT (Constraint Induced Movement therapy) has proven to be silver bullet to regain upper extremity function especially in chronic strokes [4,5]. It is a known fact that recovery of hand motor function is usually incomplete, 2/3 of patients still suffer from profoundly impaired dexterity, which significantly impacts the individual's disability and activities of daily living [6,7].

rTMS (repetitive transcranial magnetic stimulation) is a non-invasive, effective, and a painless therapeutic stimulation to modulate cortical excitability of motor area and has the potential to improve dexterity of affected hand after stroke [8,9]. High frequency rTMS over the primary motor cortex (M1) in the affected hemisphere could improve motor learning performance in patients with chronic stroke and have a positive, long-term effect on motor recovery in acute and subacute patients with stroke [10,11]. The proof of principle studies has demonstrated that the inhibitory rTMS applied over the contralesional M1 or the facilitatory rTMS applied over the M1 may improve dexterity of the affected hand following stroke [12,13].

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The ultimate aim of therapeutic strategy is the maximum restoration possible and eventual complete normalcy of function. The non-regenerative capability of the injured adult brain has been challenged in recent times and neural plasticity has been increasingly observed experimentally in both global and focal brain ischemia in animal models. Functional recovery occurs using rehabilitation measures and this functional restoration may require new synaptic connections within and away from the damaged tissue. Neuroimaging studies in stroke patients indicate altered post stroke patterns suggesting functional re-organization. It has been shown that exercises enhance neurogenesis, learning, and memory, execute function and protects age related atrophy in brain and also reported to reduce depression. These new neurons get functionally structured in the hippocampal architecture. Trans cranial magnetic stimulation (TMS) helps in yielding information on the size of the cortical reorganizational map or the speed and magnitude of MEPs after magnetic stimulators induce electrical currents using a non-invasive stimulating coil of frequency of 100 Hz. When brain is stimulated transcranially, a complex sequence of events occurs with excitatory and inhibitory effects on the corticospinal and corticobulbar pathways [13].

In this study CIMT was combined with the high frequency rTMS to assess the effect in Upper Extremity motor function post stroke. The two therapeutic strategies may be pursued to interfere with motor function of the affected hand following stroke. The objectives of the present research were to compare the efficacy of two rehabilitative regimes like CIMT and TMS for upper limb rehabilitation assessed on clinical outcomes and functional imaging. The hypothesis generated was that CIMT with TMS is more effective for optimal post-stroke upper extremity motor rehabilitation than CIMT alone.

Methods

The study was an RCT; chronic stroke patients from the hospital's neurology clinics were screened. The inclusion criterion for the study was chronic (Ischemic or haemorrhagic) stroke patients between 12 to 36 months of index event with 10° of wrist extension, 10° of thumb abduction and 10° of any two

digits extension, a score of ≥ 24 on MMSE, conscious, oriented and able to comprehend. Patients who were medically unstable, with contractures or with any wrist joint deformity, contraindications to MRI were excluded. The study was approved from IRB and written informed consent was obtained from all participants. The patients were assessed on clinical outcomes: NIHSS, fugl meyer scale, barthel index & modified rankin score, & electrophysiological outcomes: RMT (Resting motor threshold) & MEP (Motor evoked potential) at baseline, 3 weeks and 3 months [14].

A total of 100 patients were screened as per inclusion and exclusion criteria's, out of which 60 were recruited in the trial (20 were excluded & 20 refused to participate in-spite of obeying the inclusion criteria). 10 did not complete the study but were included for intention to treat analysis. The subjects were randomised into two groups using computer-based randomization method, 30 in each group. Group A received CIMT alone and Group B received CIMT with TMS for 3 weeks each.

Group A (CIMT): 30 patients in this group received only CIMT. The treatment regime for CIMT involved the good arm to be restraint from function. The unaffected arm was tied with a sling for 4-6 hours in a day while doing activities of daily living. The patient were given CIMT treatment for 1 hour by neuro-physiotherapist for 3 weeks (15 sessions) and was asked to carry out the routine exercises and activities of daily living at home for 4-6 hours using affected upper limb in that time period. The hand activities involve reaching, grasping, handling and hitting the objects. Active assisted, strengthening and motor control training is practiced by the affected arm. This purpose of exercises was to quantify the improvement in the speed and quality of movement (QOM), encouraging the tasks that were tailored to address the motor deficits of the individual patient. Modelling, prompting, and cuing of task performance, and systemically increasing the difficulty level of the tasks performed in small steps which later were transferred to home settings.

Group B (CIMT with rTMS): 30 patients in this group received CIMT (same as group A) along with high Frequency rTMS. The rTMS (repetitive transcranial magnetic stimulation) was given using magstim, rapid square 50 HZ, figure of eight air cool coil (9 cm outer wing diameter). The protocol consisted of calculation of resting motor threshold (RMT) and motor evoked potentials (MEP) of healthy and hemiplegic side before and after treatment. RMT and the motor "hot spot" of the abductor digiti minimi (ADM) muscles were evaluated according to the recommendation of the international federation of clinical neurophysiology using surface EMG monitoring. rTMS was applied over DLPFC (dorso lateral prefrontal cortex) region of the lesioned stroke hemisphere using an intensity of 120% RMT of the non-stroke hemisphere. All the patients wore ear plugs during the session. High frequency of 10 Hz, 10 second trains of 20 train's i.e, 2000 pulses with intertrain interval of 60 seconds was administered to the all patients. A total 15 sessions were given 5 days/ week for 3 weeks. Each subject in both the groups completed the scheduled sessions without any adverse effect.

Statistical analysis (Clinical outcomes)

The statistical analysis was performed using the SPSS software (version 16). At the baseline the two groups had no significant difference in age, sex, NIHSS and MMSE scores ($p>0.05$). Comparison between the two groups was assessed using the independent t-test for calculating the difference in mean scores. The intra group comparison for both the groups was done using paired t-Test at 95% confidence interval.

fMRI statistical analysis

At the first level, the image data was post processed using 't' contrast, with a $p<0.05$ (corrected) and voxel threshold fixed at 5. A random effects analysis (one sample t-test) would be used to obtain the statistically significant clusters of activation for task performance within each session. Co-ordinates of the regions of the clusters/ regions of activation were classified corresponding to Brodmann's areas (BA) [15]. Volume, slice and surface rendering were carried out for the activated brain regions.

For statistical analysis at the group level, subjects with similar paradigms were grouped together and put through a series of statistical tests at the second level, in SPM. One-sample t-test and two-sample t-test will be used to compare the results. A paired t-test was used to study statistically significant changes in clusters recruited for processing between the two sessions (Pre and post-treatment). Unless mentioned otherwise, all averaged SPMs were threshold with $|Z|^3$ 3.1 ($p<0.05$ (uncorrected) or $p<0.05$ (corrected FWE for multiple comparisons), while clusters smaller than 3 voxels was not considered.

Results

Demographics and risk factor analysis

Group A had 21males and 9 females with mean age 44.6 ± 10.4 years & group B had 17 males and 13 females with the mean age of 46.2 ± 9.02 years. In group A, 26 patients complained first ever stroke, 8 patients had onset during sleep, 9 experienced loss of consciousness, 8 had family history of HTN and Diabetes. In group-B, 24 patients complained first ever stroke, 4 patients had onset during sleep, 13 experienced loss of consciousness, 18 were diagnosed with HTN and 10 had diabetes (Table 1).

Clinical outcomes measures

The mean of clinical outcomes Barthel Index (BI) and Fugl Meyer (FM) was analyzed using the independent t-test. Between group comparison, A & B, FM showed statistically significant improvement in group B as compared to group A at 3 weeks (95%CI: -12.4 to -9.3, $p=0.003$) and 3months (95%CI : 7.4 to 4.2, $p=0.01$). Barthel index showed improvement between group A & B at 3months (95%CI: 6.4 to 2.6, $p=0.05$) but was not significant at 3 weeks ($p>0.05$). Repeated measure Anova showed that the mean groups were different at all-time points indicating some degree of improvement in all the subjects ($F=3.4$, $p=0.01$; $F=5.4$, $p=0.002$). Pre and post-test analysis also showed statistically significant improvement between baseline and 3 weeks and 3 weeks to 3months ($p<0.05$). Other clinical variables such as MRC grade for power, tone did not show significant improvement ($p>0.05$) between group A & B.

TMS variables

The group B patients were administered with rTMS and significant escalation was observed in MEP post therapy (95%CI; 3.2-4.5;$p=0.03$). The mean MEP pre therapy was 178.2+74.5 and post therapy was 232.8+98.6. The mean pre MT was 73.8+12.3 and the post mean was 71.2+9.6 (95% CI; -1.2 to 0.03; $p=0.56$).

fMRI analysis

We found an increase in the cluster counts in group analysis of patients from baseline to post treatment (3 weeks) and significant improvement in all the patients in group A (Table 3) with BA 2 & 6 being the most prominent followed by BA 36 of left cerebrum. Post treatment in group B (rTMS and CIMT) there was an increase in the activation of structures from baseline to 3 weeks ($p<0.05$). In between group analysis at 3 weeks (group B–group A), it was observed that BOLD activation showed a statistically significant number of clusters ($p<0.05$) of BA 6 (right & left), BA 19, BA 31 and some internal limbic structures like pulvinar in addition to the supplementary and premotor cortex areas (Table 4) in group B than group A (Figure 1 and 2).

Discussion

One of the salient findings of this research was that rTMS is safe and tolerable in chronic stroke. rTMS application for two weeks led to more improvement in clinical and functional recovery post stroke than only CIMT alone. Post stroke paralysis disrupts both neurophysiological and neuromotor strategies, leading to the rapid changes in transcallosal pathways which results in an imbalance in the interhemispheric inhibition in the primary cortical areas [16]. High frequency rTMS causes changes in the cortical excitability thus leading to an increase in the transcallosal inhibition from the unaffected to the affected hemisphere [16,17]. Thus the studies have suggested that focal 10Hz rTMS to the motor cortex of the affected hemisphere in conjugation with motor practice intervention will enhance the corticomotor excitability and would improve the motor performance in chronic stroke patients [18].

Table 1: Demographic, risk factor and clinical data for all patients.

Demographic and Clinical Data		
	Group A (N=30)	**Group B (N=30)**
AGE	44.6 ± 10.4	46.2 ± 9.02
GENDER (M:F)	21:09	17:13
SIDE OF LESION (L:R)	20:10	14:16
TYPE OF STROKE (I:H)	17:13	22:08
TIME SINCE STROKE	32 months	29 months
NIHSS	5.9 ± 1.7	5.6 ± 1.7
MMSE	24 ± 2.1	25.2 ± 2.3
mRS (range)	2-3	2-3
FES (Y/N)	26/4	24/6
ODS(Y/N)	8/22	4/26
LOC (Y/N)	9/21	13/17
FH (Y/N)	8/22	8/22
HTN (Y/N)	24/6	18/12
Diabetes (Y/N)	4/26	10/20
Hypercholesterolemia (Y/N)	5/25	7/23
Angina (Y/N)	5/25	3/27
Cardiac problems (Y/N)	5/25	6/24
Smoking (Y/N)	11/19	9/21
Alcohol (Y/N)	11/19	9/21
Migraine (Y/N)	12/18	14/16
Epilepsy (Y/N)	2/28	0/30

Table 2: Clinical outcomes at baseline, post intervention and follow up of both groups (A & B).

Group A	**Baseline**	**Post (3 weeks)**	**FUP (3 M)**	**Anova p-value**
	Mean ± SD	Mean ± SD	Mean ± SD	
BI	69.5 ± 4.3	83 ± 6.9	84.3 ± 11.4	0.003
FMA	34.53 ± 6.2	47.47 ± 6.1	42.5±6.03	0.04
Group B				
BI	66.17 ± 12.1	87.33 ± 11.1	91 ± 12.6	0.007
FMA	34.7 ± 6.4	51.47 ± 7.7	52.07 ± 7.6	0.000

Table 3: fMRI comparison Group A (post) - Group A Baseline (Affected hand).

Cluster	**mni coordinates(x,y,z)**	**Hemisphere**	**Area of activation**	**Brodmann Area**
40	-36 -28 -22	Left Cerebrum	Limbic Lobe	Brodmann area 36
197	-36 -30 32	Left Cerebrum	Parietal Lobe	Brodmann area 2
133	-22 -10 60	Left Cerebrum	Frontal Lobe	Brodmann area 6
5	18 4 72	Right Cerebrum	Frontal Lobe	Brodmann area 6
14	-44 -10 48	Left Cerebrum	Frontal Lobe	Brodmann area 4
12	-16 -40 -22	Left Cerebellum	Anterior Lobe	

rTMS is known for pschyiatric ailments providing a valuable tool for interventional neurophysiology applications, modulating brain activity in a targeted, distributed, cortical network so as to induce controlled manipulations in behavior. Our TMS findings suggest that the high frequency rTMS along with physiotherapy is safe, effective and it increases the cortical excitability in chronic stroke patients. It resulted in an increase in the limbic structures like pulvinar and (right & left), BA 19, BA 31 in addition to the supplementary and premotor cortex areas, although we did not assess patients on depression or anxiety scales in our subjects [19].

Similar studies done on post chronic stroke patients with upper extremity paresis using low frequency rTMS combined with intensive occupational therapy NEURO (Novel intervention using repetitive TMS and intensive occupational therapy) induced functional cortical reorganization leading motor functional recovery of the affected upper limb. The papers reported an enhancement of the cortical structures by acting directly on the underlying cortical region or through its connection with other structures. Various functional neural imaging studies and electrophysiological recordings have suggested decreased excitability of the ipsilesional cortex via transcallosal inhibition. This decreased cortical excitability has attributed to damage from glutamate receptors expression from neurons in the infarct zone [20].

rTMS in this research focuses in rebalancing the cortical excitability through stimulating the affected hemisphere M1 to improve affected hand function post stroke. In chronic stroke, the application of rTMS over the lesioned cortical area is meant to recruit or activate compensatory pathways and to promote plasticity. Ameli et al in his study done on cortical and subcortical MCA stroke used rTMS over ipsilesional M1 area and proved that it causes significant improvement of motor performance of affected hand in patients with subcortical stroke. The same was proved by Ashrafi and colleagues, that 10

Table 4: Showing the fMRI activations in Group A vs Group B FUP (Affected hand).

Clusters	mni coordinates x,y,z	Hemisphere	Activation Areas	Brodmann Areas
200	46 -42 2	Right Cerebrum	Limbic Lobe	BA
187	50 -36 -4	Left Cerebrum	Temporal Lobe	Brodmann Area 19
22	-24 -32 32	No Gray Matter found	Limbic Lobe	Brodmann area 31
110	-28 -24 36	Right Cerebrum	Frontal lobe	Brodmann area 6
147	-12 -12 74	Right Cerebrum	Frontal Lobe	Brodmann area 31
214	32 -58 24	Right Cerebrum	Limbic Lobe	Pulvinar
35	2 -56 -56	Right Cerebrum	Frontal Lobe	Brodmann area 24
101	12 -52 -58	Left Cerebrum	Temporal Lobe	Brodmann area 23
29	38 -38 22	Left Cerebrum	Sub-lobar	Brodmann area 32
11	10 8 30	Left Cerebrum	Limbic Lobe	Caudate Body
23	54 -58 4	Right Cerebrum	Limbic Lobe	Brodmann area 38
35	28 -40 -36	Right Cerebellum	Limbic Lobe	Brodmann area 37
10	36 10 -34	Frontal Lobe	Limbic Lobe	Brodmann area 6
6	38 -34 32	Parietal Lobe	Limbic Lobe	Brodmann area 6
8	46 0 30	Sub-lobar		Brodmann area 7
5	30 -56 56	Right Cerebrum	Sub-lobar	Brodmann area 13
181	-44 -16 18	Frontal Lobe/ left	Pre Frontal Lobe	Brodmann area 6

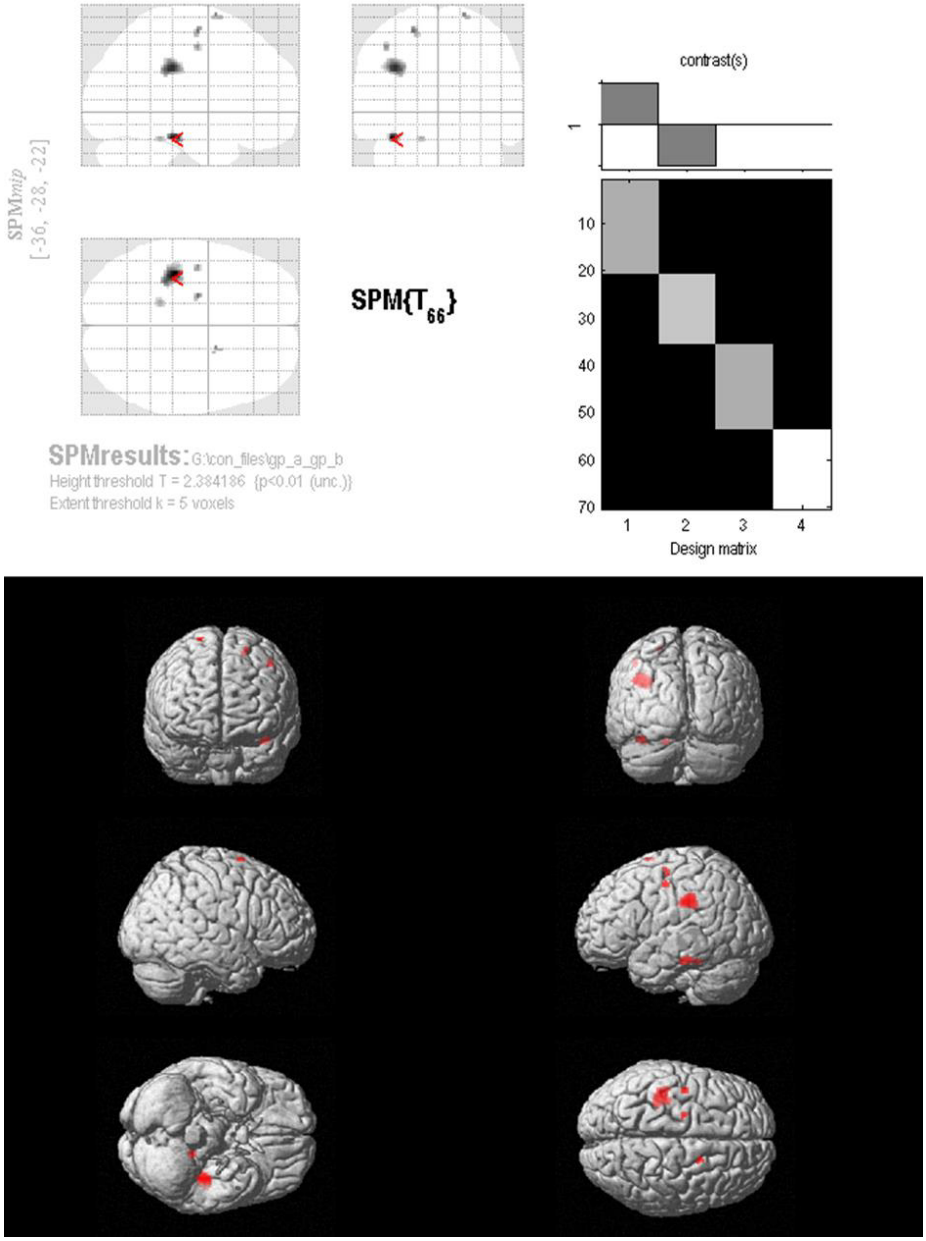


Figure 1. Showing the fMRI activations in Group A vs Group A Baseline (Affected hand).

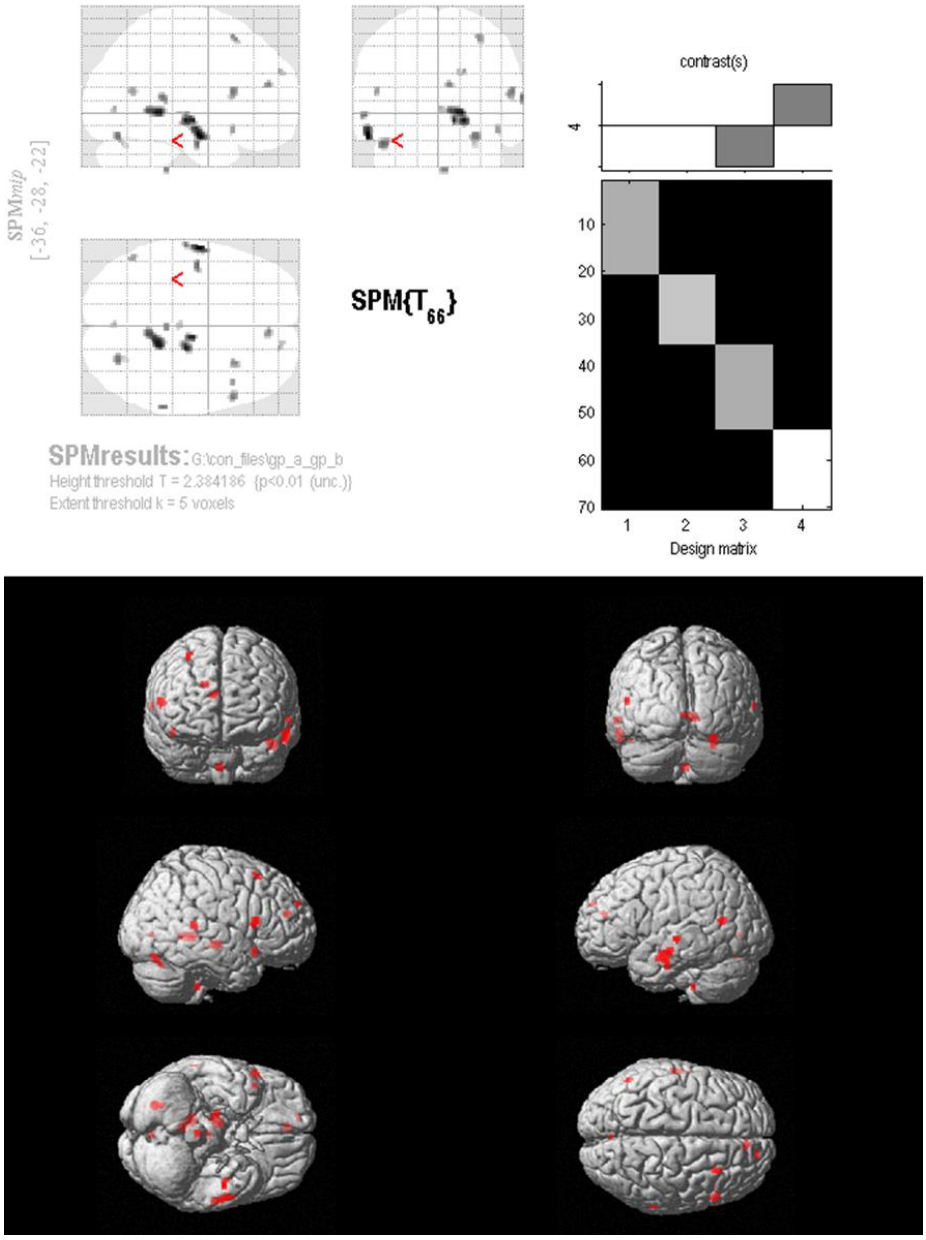


Figure 2. Showing the fMRI activations in Group A vs Group A FUP (Affected hand).

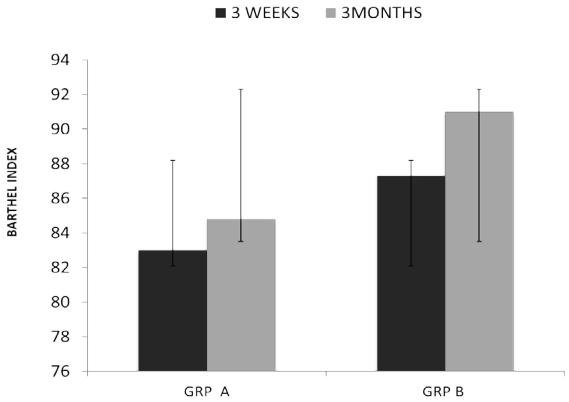
minutes session of ipsilesional rTMS of 5Hz to each subject on primary motor cortex improved motor function in patients with subcortical stroke [21]. Our study reported the same with a significant improvement in FM score at both 3 weeks and 3 monthly follow up whereas mBI showed an improvement at 3 months ($p<0.05$).

On the other hand, there have been randomised control trials, and updated reviews about CIMT and its effects on upper extremity motor recovery. Lipert and colleagues in their first report expressed changes in brain using combination of TMS & CIMT, they found that there is an increased in no. of scalp locations that produce MEP in paretic hand. The ipsilesional motor map was shown to be smaller than normal at baseline and it enlarged immediately after CIMT [22,23]. We observed a significant improvement in MEP after treatment with rTMS for 5 days a week for 3 weeks (95%CI; 3.2-4.5; p=0.03). The mean MEP pre therapy was 178.2+74.5 and post therapy was 232.8+98.6. The mean pre-MT was 73.8+12.3 and the post mean was 71.2+9.6 (95% CI; -1.2 to 0.03; p=0.56). A subset of the same study has shown the degree of map expansion correlates with improvement in some measure of motor ability after CIMT. The subsequent studies have found that CIMT has appeared to rebalance the motor representation of the hand in two brain hemispheres [24,25].

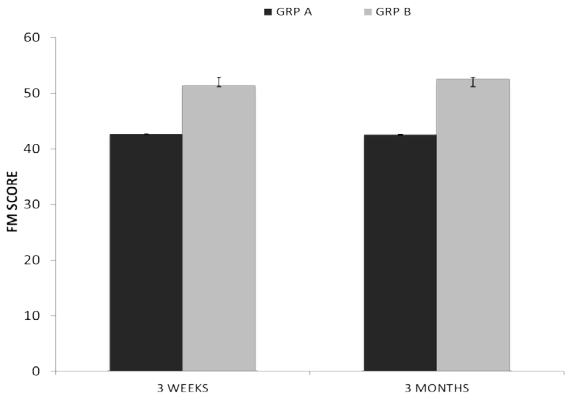
In regards to this study both the intervention techniques CIMT and rTMS were considered to have different mechanism of action to improve the cerebral function and thus improving the upper extremity motor function. The CIMT usually results in the forced use of the affected hand by constraining the non-affected extremity, thus by supressing the learned non-use pattern usually developed after stroke, on the other hand high frequency–rTMS show excitatory action on the pre motor cortex when applied over ipsilesional hemisphere. These techniques work for maximizing the brain plasticity and induce functional neural recoganization. Therefore the group having both (CIMT and rTMS) as an interventional techniques was observed to show better effect on the motor performance and functional activities of the chronic stroke patients (Graph 1and 2).

Conclusions

Our study demonstrated that high frequency rTMS over the lesioned hemisphere along with the restorative rehabilitation regime (CIMT) is more effective than CIMT alone for upper extremity functional gains. Further research with larger number of patients and longer follow-up is required to elucidate the combined effects of rTMS and CIMT.



Graph 1: Clinical outcomes Barthel Index at 3 weeks (post intervention) and 3 months (follow up) in Group A & B.



Graph 2: Clinical outcomes FM Score at 3 weeks (post intervention) and 3 months (follow up) in Group A & B.

Study Limitation

The small size of the study population did not reach statistical significance level as MEP and RMT could not be compared. The therapeutic effects of rTMS on different areas of brain could not be analysed in the present research.

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