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Effects of repetitive transcranial magnetic stimulation combined with sensory cueing on unilateral neglect in subacute patients with right hemispheric stroke: a randomized controlled study

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Abstract:

Objective: To compare the effects of rTMS combined with sensory cueing, rTMS alone, and conventional rehabilitation on unilateral neglect, hemiplegic arm functions and performance of activities of daily living.

Design: A single-blinded randomized controlled trial.

Setting: A convalescent hospital.

Subjects: Sixty inpatients with left unilateral neglect after stroke.

Interventions: Patients were randomly assigned to three groups: rTMS combined with sensory cueing, rTMS, and conventional rehabilitation alone. rTMS at 1 Hz was applied over P5 of the contralesional hemisphere while vibration cueing was emitted using a wristwatch device on the hemiplegic arm, five days per week for two weeks. The first two groups received the same dosage of conventional rehabilitation on top of their experimental interventions. Blinded assessments were administered at baseline, 2 weeks postintervention, and 6 weeks follow-up.

Main measures: Neglect and arm motor performance.

Results: Both rTMS combined with SC (99.6±33.0) and rTMS alone (88.2±28.7) significantly reduced unilateral neglect than conventional rehabilitation (72.7±33.1) when measured using the conventional subtests of the Behavioural Inattention Test, but the combination was better than rTMS alone. Hemiplegic arm functions and ADL improved in all patients across the three groups but no significant differences were found between the groups.

Conclusion: The combination of inhibitory P5-rTMS with sensory cueing was better than either rTMS or conventional rehabilitation alone in producing a stronger and long-lasting improvement in unilateral neglect, but the improvement could not be associated with arm functions and ADL.

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INTRODUCTION

Unilateral neglect is a common perceptual disorder after stroke. Patients may fail to respond appropriately to visual, auditory, and other sensory stimulation presented in the contralesional hemispace. Different treatment approaches have been established in rehabilitation with the aim of alleviating unilateral neglect but no single treatment approach has yet proven to be specific and efficient.[1] The evidence for the persistence of positive effects after intervention is also limited.[2] A combination or sequential application of different techniques for unilateral neglect can increase the therapeutic benefits compared with a single intervention, and may yield the strongest and longest-lasting effects.[3]

Repetitive transcranial magnetic stimulation (rTMS) has been shown that high- (low-) frequency rTMS can increase (inhibit) the excitability of the cortex[4]. The rationale behind rTMS is based largely on the model of interhemispheric rivalry. This suggests that both hemispheres are competing to direct attention towards the contralateral hemispace but achieve equilibrium by means of mutual inhibition; after a lesion on one side, the intact hemisphere will increase its inhibition of the damaged hemisphere, further depressing its neural activity accordingly. rTMS has been initially shown to be useful in improving unilateral neglect symptoms in poststroke patients.[5-7]

As far as the authors are aware, few studies explore whether the therapeutic effect of rTMS can be maximized by applying combining with other specific interventions on unilateral neglect. In this study, we hypothesize that rTMS will promote recovery from unilateral neglect, and that it will be more effective when combined with sensory cueing; we also propose that the affected upper extremity and activities of daily living might improve accordingly. According to our previous work, sensory cueing works as a peripheral cue to remind the patient to focus on their neglected side and affected upper limb. It is simple and easy to use with patients, and studies show that it can improve awareness of the upper extremity, and hence the arm functions, when combined with arm activation.[8] This has been proved to significantly improve the performance of tasks related to neglect in subacute stroke patients.[9] Therefore, the objective here was to compare the effects of rTMS combined with sensory cueing and conventional rehabilitation, rTMS and conventional rehabilitation, and conventional rehabilitation alone on reducing unilateral neglect and improving hemiplegic arm functions and ADL.

METHODS

Participants

Subacute patients with stroke were recruited from the rehabilitation wards of a convalescent hospital in China over a two-year period. The inclusion criteria were: (1) diagnosis of right-hemispheric stroke through neurological examination and CT or MRI scans; (2) duration since onset of more than one week; (3) presenting with unilateral neglect confirmed by the conventional subtests of the Behavioural Inattention Test[10] with cutoff scores of 129; (4) unilateral neglect as a result of recent acute stroke; (5) being aged 18 or over; and (6) Mini Mental State Examination score of ≥17.[11] Participants with poorer cognitive performance were considered to be less reliable in treatment compliance, so were excluded. Patients were also excluded if they met the following criteria: (1) duration since onset of stroke of more than six months; (2) medically unstable; (3) epileptic seizures, unconsciousness, or intracranial hypertension; (4) serious heart disease that need intensive care; (5) pregnant; (6) severe aphasia so as to have difficulty understanding the therapists' instructions; (7) metal implants *in vivo*.

This study was a single-blinded randomized controlled trial with one-month posttreatment follow-up; investigators were blinded from all assessments carried out. All patients who met the eligibility criteria were randomly assigned consecutively to the rTMS group, rTMS and sensory cueing group, or conventional training group using to a computer-generated randomization table according to random permuted blocks of four. Allocation-to-treatment sequences were concealed from all investigators responsible for carrying out the training or patients involved.

Equipment

The equipment used in the study included the TMS stimulator[a] (Yi Ruide Company, Wuhan, China) and Sensory Cueing Wristwatch[b] (SCW-V2) (PolyU Technology and Consultancy Co., Ltd., Hong Kong).

Interventions

Patients in all groups received two weeks of conventional rehabilitation. In addition, patients in the rTMS or rTMS and sensory cueing groups were exposed to low-frequency repetitive magnetic pulses generated by the TMS stimulator for two weeks. The rTMS protocol used in this study was similar to previous studies with successful results inhibitory rTMS at 1 Hz was applied over P5 (using the international EEG 10/20 system) of the contralesional hemisphere at an intensity of 90% of the individual's resting motor threshold.[6, 12] The stimulus was delivered at 900 pulses/session, with 1 session daily for 2 weeks. The resting motor threshold of each subject was measured at the first interview according to the motor-evoked potential (MEP) intensity from the right abductor pollicis brevis muscle in a resting condition. A rapid single-pulse magnetic stimulation was applied on the left primary motor area, then the investigator adjusted the output intensity to figure out the minimum stimulus intensity, This intensity which could elicit an MEP larger than 50 μV for at least 5 out of 10 consecutive trials was set as the motor threshold (MT). During positioning, the patient was required to sit in a comfortable chair when the electroencephalograph cap was put on. During treatment, the patient was required to rest in a right-side lying position on a comfortable bed, with the coil center tangentially placed over the skull.

Patients in the rTMS and sensory cueing group received an additional intervention by means of SC emitted using the device.[9] The sensory cueing protocol used was similar to our previous study.[9] The patients were asked to wear the device on their left wrist for three hours a day, five times a week, over the two weeks. The cue was given every five minutes in the form of vibration (196Hz, similar to the vibration of a cell phone) generated from the device; subjects were required to press the acknowledgement button on the device in order to stop the cueing each time it was emitted.

The 2-week conventional rehabilitation treatment consisted of 30 sessions of 45 minutes each, 2 sessions for physiotherapy sessions, and 1 occupational therapy session daily, for 5 days per week. Patients in the control group received conventional rehabilitation treatment only. All treatments were delivered at the rehabilitation centre of the participating hospital.

Outcome measurements

Firstly, information was collected on the participants' demographic characteristics and medical history. All assessments were administered at baseline (on the day before intervention), 2 weeks postintervention (immediately after 2-week treatment), and at 6 weeks follow-up (i.e. one month after completion of training). They were conducted by a separate evaluator who was blinded to the treatment and group allocation.

There were 2 primary outcome measures: (1) The conventional subtests of the Behavioural Inattention Test[10] were used for the assessment of unilateral neglect. We added the scores of the first and second three subtests to make up cancellation and drawing subscores. (2) The Catherine Bergego Scale[13] was used as an assessment of day functioning for unilateral neglect.

Secondary outcome measures included: (1) The functions of the hemiplegic upper limb were measured using the Fugl-Meyer Assessment[14] upper extremity subscore, (2) the Action Research Arm Test[15], and (3) The Modified Barthel index.[16]

The research procedure was approved by the human ethics committee of the Hong Kong Polytechnic University (Ref. no.: HSEARS20130720002) and the West China Hospital of Sichuan University (no.201363). All participants completed and signed an informed written consent form before enrollment in this study. The clinical trial registration number (URL: http://www.clinicaltrials.gov) is: NCT02645344.

Statistical analysis

An intention-to-treat analysis was applied to compare the outcomes. The 'last observation carried forward' method was used; that is, if a subject dropped out, missing values were replaced by the last assessment score of that variable. Demographic and baseline characteristics were compared using analysis of variance (ANOVA; continuous and ordinal data) or chi-square tests (categorical data). Two-way repeated measures ANOVA tests were used to compare the between- (group effects) and within-subject effects (time effects) as well as the interaction effects (group×time effect) on both primary and secondary outcomes. Additional ANOVA analyses were also performed on the cancellation and drawing subscores. Tukey's HSD (Honestly Significant Difference) *post hoc* test was used for post-ANOVA pairwise comparisons if needed. Significance was set to 0.05 (two-tailed). All statistics were calculating using SPSS 21.0 software and the analysis was undertaken by the investigators in a non-blinded fashion.

RESULTS

Figure 1 shows the flow of participants. A total of 196 right-hemispheric stroke patients were screened for eligibility, of whom 75 were identified as having unilateral neglect. A total of 60 patients were recruited to the study according to the criteria set out above. Subjects were randomly allocated to one of the three groups (control n=20; rTMS n=20, rTMS and sensory cueing n=20). Four patients were lost in the follow-up. Across the whole study, no subjects reported severe side effects. No discomfort was reported across all experimental groups.

Data from 60 patients were used in the final analysis. The mean age of all participants was 58.0±12.3 years, and the average duration after onset of stroke was 41.9±39 days. Most were male (72%) and ischemia was the main type of stroke sustained (68%). There were no significant differences between the three groups in terms of demographic and baseline characteristics (Table 1).

For the primary outcomes, all patients significantly improved in unilateral neglect across the three occasions as measured using the Behavioural Inattention Test ($F_{2, 114}$=123.738, p<0.01,η^2=0.685) at both postintervention ($F_{1, 57}$=119.608, p<0.01,η^2=0.677) and follow-up phases ($F_{1, 57}$=149.1, p<0.01,η^2=0.723). There was a significant time × group interaction ($F_{2, 114}$=123.982, p<0.01,η^2=0.230).

There were no overall between-group effects, but the overall between-subjects tests reported a medium effect size (η^2 =0.076). *Post hoc* analyses showed that the Behavioural Inattention Test scores of the rTMS and sensory cueing group significantly improved at both immediate postintervention (p=0.025) and follow-up (p=0.003) compared to the control group. The rTMS group showed a significant improvement only at follow-up in relation to the control group (p=0.048). There was a trend for higher mean scores in the Behavioural Inattention Test for the rTMS and sensory cueing group than those receiving rTMS alone, but no significant differences could be identified between the two groups at either postintervention or follow-up.

Additional analyses were conducted to compare the cancellation and drawing scores. The results for the former were similar to those for the Behavioural Inattention Test, while no significant improvement was found in the drawing tasks between the rTMS plus sensory cueing and control groups at postintervention (p=0.062) and follow-up (p=0.141) The mean scores for the Behavioural Inattention Test, cancellation, and drawing scores across all three occasions are presented in Figure 2. No significant between-group differences were found in the Catherine Bergego Scale except for the overall time effect ($F_{2, 114}$=123.982, p<0.01, η^2=0.685).

No overall significant difference in group effects and time×group interaction effects, except for time effects, were observed for the FMA ($F_{2, 114}$=37.454, p<0.001,η^2=0.397), ARAT ($F_{2, 114}$=16.127, p<0.01, η^2=0.221) or MBI ($F_{2, 114}$=113.441, p<0.001,η^2=0.666). All patients improved in both arm function and accompanied activities of daily living over time, but the improvement in arm function for the control group was less than for the other two groups. No differences were found across the three groups in any of the secondary outcomes across the three occasions (Table 2).

DISCUSSION

The results of this study suggest that inhibitory P5-rTMS combined with sensory cueing maybe better than rTMS alone in improving unilateral neglect, based on the Behavioural Inattention Test postintervention scores. In terms of long-lasting effects, both the rTMS plus sensory cueing and rTMS groups performed significantly better than the conventional rehabilitation, but no significant difference was found between the two. Unlike our previous study,[9] the results did not indicate a significant difference between performance on the neglect drawing and cancellation tasks.

Studies of low-frequency rTMS show promising results in terms of unilateral neglect rehabilitation through inducing and restoring the interhemispheric balance. In our study, rTMS can be characterized as a top-down treatment approach, whereas sensory cueing is a bottom-up intervention.[3] The inhibitory rTMS focuses on rebalancing the excitability between the hemispheres through a top-down pathway, while sensory cueing aims at increasing the attention paid to the neglected side, with the external signals emitted from the wristwatch device increasing the efferent inputs from the hemiplegic limb. The combination of both rTMS and sensory cueing increases the arousal state of the ipsilesional hemisphere to be equivalent to that of the unaffected side. Although there was no significant difference in long-lasting effects between the rTMS and rTMS plus sensory cueing groups at follow-up, the combined group had higher mean scores in the Behavioural Inattention Test than those receiving rTMS alone. The statistical power of this was less than 60%, which meant that the potential difference might be detected if the sample size was big enough.

With the recent development of neuroimaging and transcranial magnetic stimulation, researchers have suggested that the interhemispheric imbalance of excitability in the frontoparietal networks induced by interhemispheric rivalry is the central pathophysiological mechanism underlying unilateral neglect.[17-19] Restoration and rebalancing of cortical excitability within the attentional network, thus, is important in the acute phase after stroke.

Attentional modulations can be divided into the domain-specific and domain-independent.[20] The latter, in our experimental intervention the low-frequency rTMS, reduces the increase in attention over the unaffected hemisphere through the top-down influence of the cerebral cortex and thus induces a synchronization of the attentional modulations over both hemispheres, without displaying any selectivity for sensory modality or cognitive domain. Accordingly, the primary somatosensory cortex in the domain-specific attentional modulation becomes responsive to arousal levels when the patient attends to (or is aroused by) the vibration stimulus from the sensory cueing wristwatch on the affected arm. The findings may imply that both domain-specific and domain-independent attentional modulations are necessary for the spatial attention indicative of the global impairment of the attention network found in unilateral neglect. This is also consistent to the recommendation that rTMS may be considered as an adjunct to remedial-based techniques in treatment of unilateral neglect.[21]

Although our experimental interventions led to improvement at the impairment level, no significant results were observed at the functional level when measured using the Catherine Bergego Scale. This result is consistent with that of a previous review showing that reduction in unilateral neglect could not be generalized into gains in functional independence.[2] This study also explored the secondary effects on hemiplegic upper limb functions and activities of daily living associated with unilateral neglect. All patients significantly improved in terms of arm functions and daily independence across the three occasions, as measured using the Fugl-Meyer Assessment, the Action Research Arm Test, and the Modified Barthel Index. Unfortunately, no significant between-group differences were found. The positive effect of using low frequency contralesional rTMS alone in reduction of unilateral neglect in our study was similar to a recent study comparing rTMS with a sham, in contrast, no advantage over conventional rehabilitation in improving arm functions could be found in our study.[22]

This study had some limitations, including the absence of sham rTMS stimulation. The rTMS both alone and in combination with sensory cueing was delivered on top of conventional rehabilitation; the additional treatment time favored the two experimental groups over the control group that received conventional rehabilitation only. The rTMS combined with sensory cueing group also benefited by an additional time comparing to rTMS alone group. It would have been interesting to study the adjuvant effect of rTMS by including a group receiving only sensory cueing and conventional rehabilitation.

The absence of sham sensory cueing for comparison was also a limitation in this study, although sham sensory cueing has been done on a previous study.[9] In addition, all subjects were recruited from a single trial site, so sampling bias was another confounding factor. Although there was no statistical significant difference among 3 groups in baselines, conventional group vs. other 2 groups had some difference in the time since onset (Table 2). The sample size was not big enough for a subgroup analysis to be performed in order to determine which subtype of unilateral neglect or brain lesions was more sensitive to these interventions.

(Words: 2,677)

CLINICAL MESSAGES

- A combination of low frequency P5-rTMS (1Hz) with sensory cueing may reduce the symptoms of unilateral neglect compared with rTMS or conventional rehabilitation alone, and may yield a stronger and longest-lasting effect.

- The use of inhibitory P5-rTMS or rTMS combined with sensory cueing is not more effective than conventional rehabilitation in improving ADL and arm function for patients with right hemispheric stroke.

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Authors' Note

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Declaration of Conflicting Interests

The authors have no disclosure of any commercial interest relevant to the subject of this manuscript except disclosure of patents of SCW-V2 (US patent: US-2010-0160834-A1 and Chinese patent: 200910175541.7).

Equipment

a. Model CCY-1, Yi Ruide Company, Wuhan, China.

b. Model SCW-V2, PolyU Technology and Consultancy Co., Ltd., Hong Kong.

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Table 1 Comparison of demographic and baseline characteristics

	Control group (n=20)	rTMS＋SC group (n=20)	rTMS group (n=20)	p
Demographics				
Age (y), mean±SD	58.7±12.7	54.6±11.8	60.7±12.2	0.28
Gender – Female (%)	3 (15%)	6(30%)	8(40%)	0.21
Comorbidities				
Hypertension, n%	10(50%)	12(60%)	12(60%)	0.76
Diabetes, n%	5(25%)	2(10%)	8(40%)	0.09
Heart disease, n%	3(15%)	1(5%)	4(20%)	0.50
Stroke characteristics				
Time since onset (d), mean±SD	42.5±30.6	36.6±33.2	37.5±26	0.84
Type				
Ischemic (n,%)	13(65%)	12(60%)	16(80%)	0.36
Hemorrhagic (n,%)	7(35%)	8(40%)	4(20%)	
Cognition (MMSE) , mean±SD	21.2±5.5	23.4±3.8	22.7±4.4	0.31
FTHUE-HK	1.3±0.9	1.7±1.2	1.7±1.1	0.51
Involved brain sites, n (%)				
Frontal lobe	14(70%)	11(55%)	13(65%)	0.61
Temporal lobe	17(85%)	12(60%)	15(75%)	0.19
Parietal lobe	14(70%)	9(45%)	13(65%)	0.23
Occipital lobe	6(30%)	2(10%)	3(15%)	0.24
Insular lobe	10(50%)	4(20%)	8(40%)	0.13
Basal ganglia	11(55%)	13(65%)	13(65%)	0.75
Thalamus	3(15%)	1(5%)	3(15%)	0.52
Primary outcomes, mean±SD				
BIT-C	58.4±31.0	59±35.3	56.0±32.2	0.76
Cancellation tasks	56.1±29.5	55.5±32.8	54.0±30.4	0.39
Drawing tasks	2.4±2.6	3.5±4.1	3.0±2.9	0.57
CBS	20.5±5.8	18.5±6.8	21.2±6.5	0.82
Secondary outcomes, mean±SD				
FMA	7.6±12.5	8.9±14.6	9.5±14.2	0.90

ARAT	2.2±7.6	4±9.8	4.0±8.2	0.75
MBI	33.3±18.4	33.3±16.6	26.7±10.8	0.31

Note: y=year; d=day; MMSE = Mini Mental State Examination; BIT-C = conventional subtests of the Behavioural Inattention Test; CBS = Catherine Bergego Scale; FTHUE-HK = the Hong Kong version of the Functional Test for the Hemiplegic Upper Extremity; FMA = Fugl-Meyer Assessment; ARAT = Action Research Arm Test; MBI = Modified Barthel index.

Table 2 Comparison of outcomes for all three groups across three occasions

Outcomes	Control group (n=20)	rTMS+SC group (n=20)	rTMS group (n=20)	F	p@
BIT-C					
Baseline	58.4±31.0	59.0±35.3	56.0±32.2		
Posttreatment	72.7±33.1#	99.6±33.0#◆	88.2±28.7#	3.64	0.032
Follow-up	76.7±33.2#	108.8±27.1#·	99.0±26.5#◆	6.38	0.003
BIT-Cancellation tasks					
Baseline	56.1±29.5	55.5±32.8	54.0±30.4		
Posttreatment	69.1±31.3#	93.4±30.4 #◆	83.5±26.8#	3.44	0.039
Follow-up	71.9±30.6#	101.6±24.7#·	93.5±24.1#◆	6.63	0.003
BIT-Drawing tasks					
Baseline	2.4±2.6	3.5±4.1	3.0±2.9		
Posttreatment	3.7±2.8·	6.2±4.1#	4.7±3.5#	2.71	0.075
Follow-up	4.8±3.7#	7.2±4.0#	5.5±4.1#	1.94	0.154
CBS					
Baseline	20.5±5.8	18.5±6.8	21.2±6.5		
Posttreatment	17.9±6.5#	14.1±7.0#	16.4±5.8#	1.77	0.180
Follow-up	15.7±6.6#	11.2±6.4#	13.9±5.2#	2.77	0.071
FMA					
Baseline	7.6±12.5	8.9±14.6	9.5±14.2		
Posttreatment	11.5±16.8	12.4±15.5#	13.0±16.0#	0.05	0.955
Follow-up	15.2±17.7#	15.7±16.5#	17.7±18.4#	0.11	0.894
ARAT					
Baseline	2.2±7.6	4.0±9.8	4.0±8.2		
Posttreatment	3.9±10.4	5.4±11.3*	5.3±9.6#	0.12	0.884
Follow-up	5.3±13.1	7.1±13.0#	7.0±12.4#	0.13	0.879
MBI					
Baseline	33.3±18.4	33.3±16.6	26.7±10.8		
Posttreatment	43.9±19.7#	47.0±14.4#	40.5±14.2#	0.79	0.461
Follow-up	54.7±23.2#	60.7±17.0#	55.2±17.1#	0.59	0.556

Note: @ Between-subject effects among the three groups: ◆$p<0.05$, ·$p<0.01$ compared with control group (ANOVA followed by post hoc test using Tukey HSD); Within-subjects effects: *$p<0.05$, #$p<0.01$ compared with baseline; BIT-C = conventional subtests of the Behavioural Inattention Test; CBS = Catherine Bergego Scale; FMA = Fugl-Meyer Assessment; ARAT = Action Research Arm Test; MBI = Modified Barthel index.

Figure 1 CONSORT flow diagram of patients recruited to the study

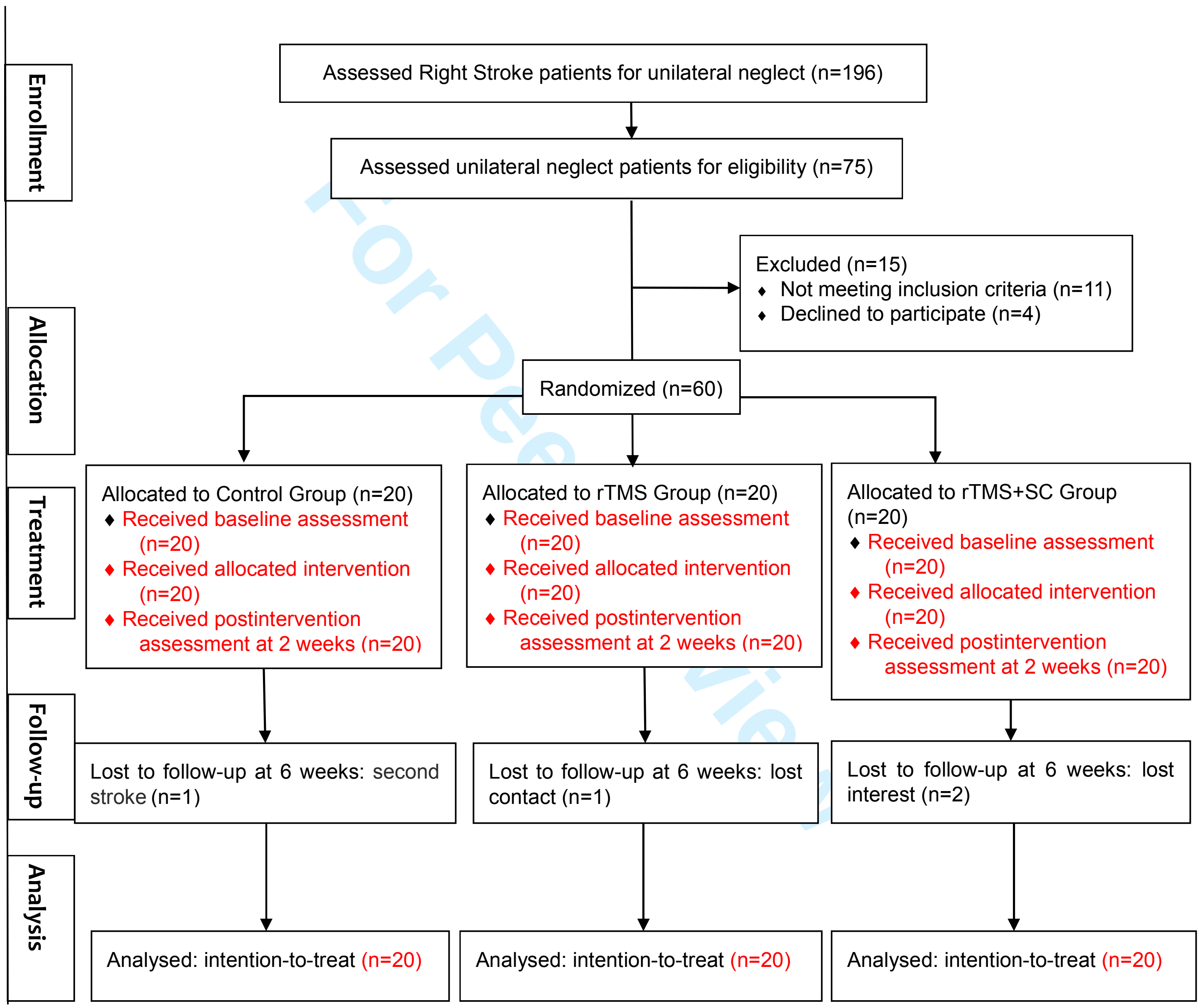
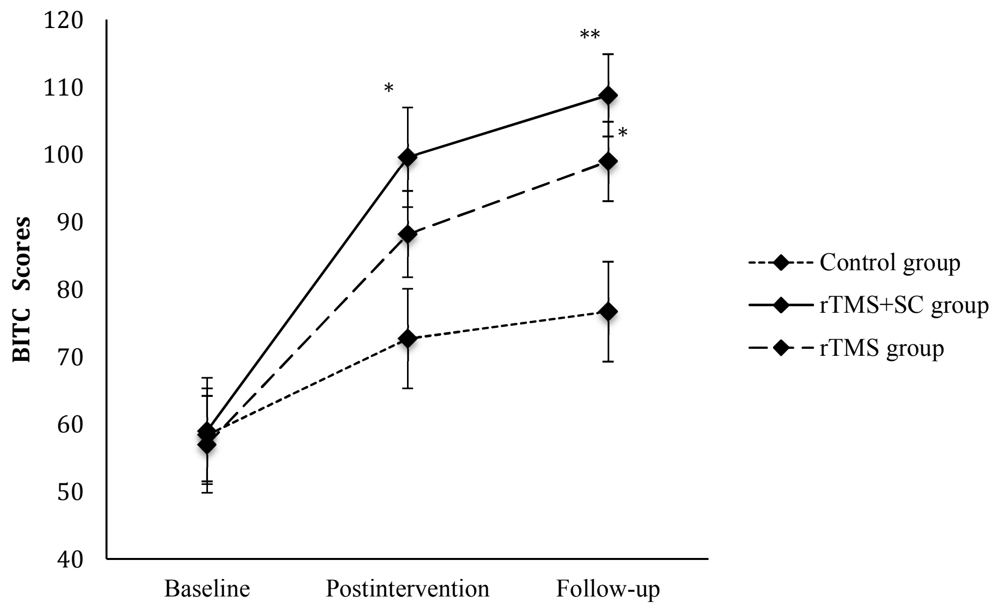
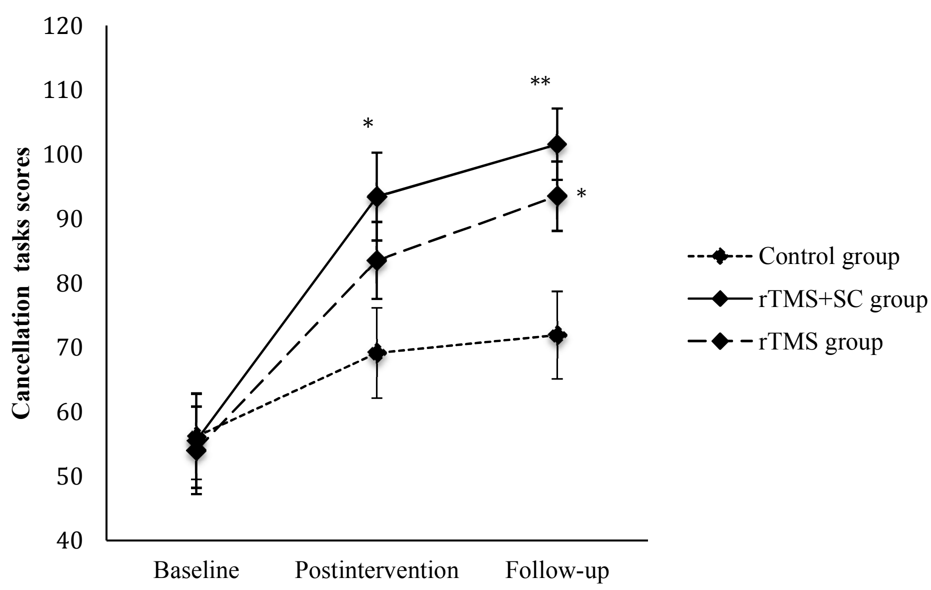


Figure 2 Conventional subtest scores for the BIT

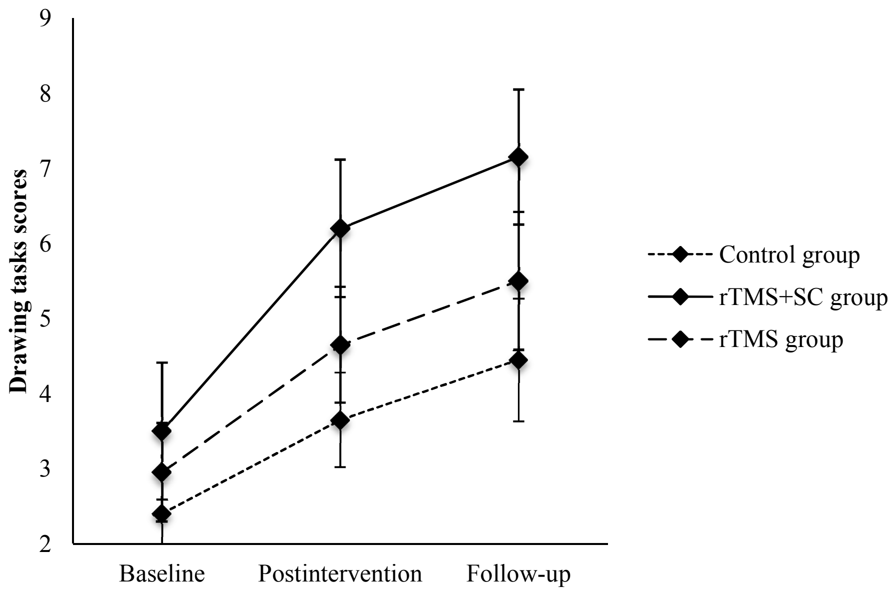
A)



B)



C)



Note: (A) total score for the conventional subtests of the Behavioural Inattention Test; (B) scores for the cancellation tasks; (C) scores for the drawing tasks. Error bars represent (SEM); Asterisks indicate p values <0.05 when compared with the control group; double asterisks indicate p values <0.01 when compared with the control group.