E-ISSN: 2833-3772 | Volume 3 (2024), Issue 5 | Sep-Oct 2024

The Scientific Journal of Medical Scholar

Publisher: Real-Publishers Limited (Realpub LLC)
30 N Gould St Ste R, Sheridan, WY 82801, USA
Associate-Publisher: SSESD, Egypt
Website: https://realpublishers.us/index.php/sjms/index

The Scientific Journal of Medical Scholar

Available online at Journal Website
https://realpublishers.us/index.php/sjms/index
Subject (Neurology)

REALPUB LLC

Original Article

Prediction of Aphasia Outcome Using Low Frequency Transcranial Magnetic Stimulation in Post-Stroke Non-Fluent Aphasia

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Article information

Submitted: October 4th, 2024; Accepted: October 19th, 2024; DOI: 10.55675/sjms.v3i4.113

Citation: Saber SM, Hammad AB, Sallam YA, Ahmed SF, Mawad HA. Prediction of Aphasia Outcome Using Low Frequency Transcranial Magnetic Stimulation in Post-Stroke Non-Fluent Aphasia. SJMS 2024; 3 (5) Sep-Oct: 112-118. DOI: 10.55675/sjms.v3i4.113

ABSTRACT

Background: Stroke, a global health concern, often leads to language impairment (aphasia). In Egypt, with a high stroke prevalence, aphasia affects a significant number of survivors. Noninvasive techniques like repetitive transcranial magnetic stimulation (rTMS) show promise in rehabilitation. Cultural variations in test results emphasize the need for region-specific considerations in standardized assessments for post-stroke care. Aim of the work: To evaluate the role of low frequency rTMS to speed up the recovery of post-stroke aphasia for a better quality of life.

Patients and Methods: This randomized clinical trial investigates the effects of (rTMS) on post-stroke aphasia. Patients with post-stroke non-fluent aphasia were divided into two groups, with one receiving inhibitory rTMS and the other sham sessions. Inclusion criteria involve adults with a single left hemisphere stroke, while exclusion criteria include prior strokes. The study includes comprehensive assessments for aphasia, and depression. The stimulation protocol involves 20 minutes of daily rTMS for ten days, targeting the right inferior frontal gyrus. The study aims to evaluate the rTMS impact on language recovery.

Results: The study evaluated low-frequency rTMS for post-stroke aphasia recovery in 30 patients, comparing TMS and sham groups. No significant demographic or cerebrovascular risk factor differences were found. While rTMS group showed improvement in depression, there were no significant differences between TMS and sham groups in aphasia improvement.

Conclusion: Low-frequency rTMS demonstrated no significant superiority over sham stimulation in post-stroke aphasia recovery. Both groups exhibited improved depression without notable distinctions.

Keywords: Non-fluent Aphasia; Outcome; Prediction; Low-frequency; Transcranial Magnetic Stimulation; Post-stroke.

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INTRODUCTION

Stroke arises from an abrupt interruption of blood flow to the brain, leading to a rapid onset of neurological dysfunction that persists beyond 24 hour[1]. Ischemic strokes, caused by blood clots (88%), are the most prevalent type, followed by intracerebral hemorrhage (9%) and subarachnoid hemorrhage (3%)[2]. Ranking second only to heart disease, stroke is a global burden, causing significant death and disability. New stroke cases have nearly doubled since 1990, exceeding 13 million individuals annually [3].

Egypt, a populous low-middle-income nation in the Middle East, has a high stroke prevalence (963/100,000) contributing to 6.4% of deaths [4]. Strokes, often affecting the left hemisphere of the brain responsible for language in right-handed individuals, are the leading cause of aphasia, a language disorder. One-third of stroke survivors experience aphasia, with varying degrees of severity across speech, comprehension, reading, writing, and gestural communication [5].

Aphasia, an acquired impairment of language following brain damage (distinct from communication difficulties due to sensory loss or dementia), is typically associated with strokes [5]. Two broad categories exist: fluent aphasia and non-fluent aphasia (also called expressive aphasia). Broca's aphasia, transcortical motor aphasia, and global aphasia fall within the non-fluent category [6].

Brain lesions causing aphasia significantly impair communication, impacting long-term well-being for patients and families[7]. Aphasia reduces functional ability, and mood, hindering participation in daily activities and work reintegration. Given its prevalence following stroke, QoL in aphasic patients remains a major concern and a target for rehabilitation efforts. Promising results over the past two decades suggest that non-invasive brain stimulation techniques, particularly transcranial magnetic stimulation (TMS), can be beneficial for aphasia rehabilitation after stroke [8].

rTMS emerges as a promising, non-invasive approach for post-stroke aphasia rehabilitation[8]. This technique safely modulates brain plasticity, a process crucial for recovery, with effects lasting days to months[9]. rTMS painlessly delivers a magnetic field, inducing electrical currents within targeted neurons. These currents can alter cortical excitability, potentially leading to long-lasting neuroplastic changes. While the role of the right hemisphere in language recovery remains debated, rTMS can promote beneficial recruitment of perilesional areas in the dominant hemisphere, damaged by stroke, fostering potential for recovery [10].

Post-stroke aphasia rehabilitation faces challenges due to persistent deficits beyond the initial recovery window [11]. rTMS offers promise by modulating cortical plasticity, a mechanism underlying recovery [8]. Tailoring stimulation frequency (low for suppression, high for excitation) targets specific brain areas to promote functional recruitment [10, 12]. However, cultural variations necessitate caution in standardized aphasia test interpretation[13]. Furthermore, stroke's impact extends beyond language, frequently causing cognitive impairments that hinder rehabilitation efforts[14]. Elucidating the relationship between language and cognition in aphasia could pave the way for more holistic rehabilitation strategies [15]. This study investigates the potential of low-frequency rTMS to accelerate post-stroke aphasia recovery, aiming to improve patients' quality of life.

PATIENTS AND METHODS

This randomized, controlled, parallel clinical trial evaluated the effects of contralesional low-frequency rTMS on post-stroke aphasia. Patients with non-fluent aphasia were recruited from the neurology outpatient clinic at Al-Zahraa University Hospital between December 1st, 2022, and July 1st, 2023.

Grouping:

The study employed a two-arm parallel design. Group A (TMS group) received active, inhibitory low-frequency rTMS (1 Hz, 90% motor threshold) targeted at the contralesional hemisphere. Group B (sham group) underwent sham rTMS using an inverted coil over the same region for a similar duration.

Randomization:

Simple coin randomization allocated participants equally to the TMS and sham groups. Both groups received rTMS in separate rooms at different times to minimize communication and potential bias. While complete investigator blinding was not achievable due to the nature of the intervention delivery and assessment, participants remained unaware of their group assignment throughout the study.

Inclusion criteria:

This study recruited right-handed, Arabic-speaking adults (aged >18 years) who suffered a single left-hemisphere ischemic stroke (6 months to 3 years post-onset) confirmed by MRI or CT. Patients had normal pre-stroke language function and no history of neurological disorders, cognitive decline, or contraindications to TMS. Exclusion criteria included non-native Arabic speakers, left-handedness, prior stroke, severe dysarthria, and other conditions affecting cooperation or safety (e.g., dementia, seizures, metal implants).

Medical assessment:

A comprehensive assessment was conducted on all participants. This included a detailed medical history focusing on demographics, risk factors (hypertension, diabetes, dyslipidemia, heart disease, and smoking), cognitive status, medications, and implanted devices (A.I). A full physical and neurological examination followed (A.II). Visual and auditory function were screened, with detailed audiological evaluation performed when necessary (A.III). TMS eligibility was confirmed using a standardized checklist (A.IV.B). Additionally, all participants underwent brain imaging (CT scan or MRI) if not already available (B).

Aphasia assessment:

The Comprehensive Aphasia Test (CAT) was employed to assess aphasia severity across language modalities (production, comprehension). This standardized tool, grounded in cognitive neuropsychology, evaluates not only core language functions but also associated cognitive skills relevant to rehabilitation. It provides therapists with a comprehensive profile of strengths and weaknesses, guiding treatment planning and monitoring progress over time.

Depression assessment:

The Stroke Aphasic Depression Questionnaire-10 (SADQ-10) was used to assess depressive symptoms. This validated 10-item tool, derived from the SADQ-21, offers improved accuracy in detecting depression compared to the original version. Scores range from 0 to 30, with scores above 14 indicating a likelihood of depression.

Stimulation protocol:

Patients in the TMS group received 20-minute sessions (1200 pulses at 1 Hz) of low-frequency rTMS daily for 10 days, delivered in two blocks of five consecutive days separated by two rest days. The target area was the right inferior frontal gyrus (F4 according to the 10/20 EEG system), chosen based on prior research demonstrating its efficacy in rTMS treatment. Both active and sham stimulation employed a figure-eight coil with a diameter of 70 mm.

Sham stimulation:

The sham stimulation group served as a placebo control, utilizing a coil identical in shape and sound to the real coil but lacking a magnetic field. This ensures no cortical activation occurs during sham sessions, effectively controlling for non-specific effects like the clicking sound or therapist interaction. By comparing outcomes between the TMS and sham groups, the study can isolate the specific effects of low-frequency rTMS on aphasia recovery.

Evaluation and Follow up:

Adherence was monitored through bi-weekly phone calls to assess general health and confirm evaluation appointments. All participants underwent assessments for aphasia severity and depression using standardized tools, both before and immediately following the rTMS intervention.

Statistical analysis:

Statistical analysis was performed using SPSS software (version 23.0). Normally distributed data (assessed by Kolmogorov-Smirnov and Shapiro-Wilk tests) are presented as mean ± standard deviation and range. Non-normally distributed data are presented as median with interquartile range (IQR). Categorical data are presented as frequencies and percentages.

RESULTS

This study employed 30 participants equally divided into two groups: a TMS group (n=15) and a sham group (n=15). Baseline demographic characteristics, including age, sex, occupation, residence, and handedness, were non-significant between the TMS and sham groups with *p*-value= 0.151, 0.66, 0.46, 0.71, 1.0 respectively **(Table 1)**.

In addition, there is no statistically significant difference between TMS group and sham group regarding the duration of CVS disability (*p*-value=0.92) **(Table 2)**. Regarding radiological findings, there is no significant differences were observed between the TMS and sham groups in terms of infarction type, side, or location **(Table 3)**.

Aphasia assessment

The CAT assessment revealed no significant differences between the TMS and sham groups in pre- and post-intervention cognitive screening or language comprehension scores. However, the sham group performed significantly better on subtests assessing repetition, naming, and reading compared to the TMS group. Furthermore, no statistically significant improvements were observed in total CAT scores or any sub-scores (cognitive, comprehension, or expressive language) within either group following rTMS **(Table 4)**.

Depression assessment

The SADQ scores revealed no significant differences in depression severity between the TMS and sham groups before the intervention. However, the TMS group exhibited a statistically significant improvement in SADQ scores compared to the sham group after intervention, suggesting a potential benefit of rTMS in reducing post-stroke depression **(Table 5)**.

Correlation between duration of CVS disability and percentage of improvement of CAT and SADQ in TMS group, using Pearson's correlation coefficient (r).

There was a statistically significant positive correlation between duration of CVS disability "years" and percentage of improvement of spoken language, with p-value ($p<0.05$), while statistically negative correlation between duration of CVS disability "years" and percentage of improvement of writing, with p-value ($p<0.05$) **(Table 6)**.

Table (1): Comparison between TMS group and sham group regarding Demographic data

	Demographic data	TMS group (n=15)	Sham group (n=15)	Test value	p-value
Age (years)	Mean±SD	51.80±14.39	58.00±7.60	2.178	0.151
	Min. – Max.	28-74	48-70		
Sex (n,%)	Female	4 (26.7%)	3 (20.0%)	0.186	0.666
	Male	11 (73.3%)	12 (80.0%)		
Occupation	Housewife	4 (26.7%)	3 (20.0%)	2.552	0.466
	Manual worker	4 (26.7%)	3 (20.0%)		
	Not working	3 (20.0%)	7 (46.7%)		
	Office worker	4 (26.7%)	2 (13.3%)		
Residence	Rural area	8 (53.3%)	7 (46.7%)	0.133	0.715
	Urban	7 (46.7%)	8 (53.3%)		
Handedness (n,%)	Right - handed	15 (100.0%)	15 (100.0%)	0.000	1.000

Table (2): Comparison between TMS and sham groups regarding duration of CVS disability

Duration of CVS disability	TMS group (n=15)	Sham group (n=15)	Test value	p- value
6-12 months	7 (46.7%)	6 (40.0%)	0.168	0.92
1-2 years	5 (33.3%)	6 (40.0%)		
2-3 years	3 (20.0%)	3 (20.0%)		

Table (3): Comparison between TMS and sham groups regarding radiological data

MRI or CT brain		TMS group (n=15)	Sham group (n=15)	Test value	p-value
Infarction type (n,%)	Non-Lacunar	15 (100.0%)	15 (100.0%)	0.0001	1.000
Infarction side (n,%)	Left	15 (100.0%)	15 (100.0%)	0.0001	1.000
Infarction Site(n,%)	Cortical	9 (60.0%)	11 (73.3%)	0.600	0.439
	Subcortical	6 (40.0%)	4 (26.7%)		

Table (4): Percentage of improvement of SADQ (before and after TMS stimulation).

CAT			TMS group (n=15)	Sham group (n=15)	Test value	p- value
TMS stimulation (cognitive screen)	Before		26.40±9.08	26.60±8.60	0.004	0.951
	After		25.13±7.65	26.60±8.05	0.247	0.623
	% of improvement		0.03%±0.02%	0%±0%		
	Paired comparison	t-test, p	1.669, 0.117	0.001, 1.00		
Language comprehension (spoken and written language)	Before		42.07±12.64	47.53±10.51	1.064	0.311
	After		43.80±6.37	47.60±10.52	0.572	0.456
	% of improvement		3%±1%	0%±0%		
	Paired comparison	t-test, p	0.929, 0.369	0.001, 1.00		
Written language	Before		28.27±9.80	36.13±8.69	1.245	0.274
	After		29.07±11.21	36.13±13.69	0.982	0.330
	% of improvement		1%±0%	0%±0%		
	Paired comparison	t-test, p	0.414, 0.685	0.001, 1.00		
Expressive language	Before		29.47±9.31	39.27±11.73	2.148	0.031*
	After		29.60±8.26	39.27±9.73		
	% of improvement		0%±0%	0%±0%		
	Paired comparison	t-test, p	0.086, 0.933	0.001, 1.00		
Naming	Before		19.07±6.37	35.47±10.31		
	After		20.67±6.68	35.47±8.31		
	% of improvement		3%±0%	0%±0%		
	Paired comparison	t-test, p	1.129, 0.278	0.001, 1.00		
Reading	Before		13.40±3.65	22.13±5.26		
	After		12.67±3.85	22.80±5.79		
	% of improvement		1%±0%	0.67%±0.16		
	Paired comparison	t-test, p	0.728, 0.478	0.672, 0.387		
Writing	Before		25.27±7.23	33.67±8.17		
	After		24.60±7.34	29.31±3.81		
	% of improvement		1%±0%	4.4%±3%		
	Paired comparison	t-test, p	0.392, 0.701	1.863, 0.097		

Table (5): Comparison between TMS group and sham group regarding SADQ.

SADQ	TMS group (n=15)	Sham group (n=15)	Test value	p-value
Before TMS stimulation	11.27±4.04	12.67±4.39	0.826	0.371
After TMS stimulation	11.87±3.40	12.67±4.39	0.312	0.581
Percentage of improvement of SADQ within each studied group before and after TMS stimulation.				
Mean±SD	5.30%±1.92	0.00%±0.00		
Paired sample test (p-value)	P=0.043*	P=1.000		

Table (6): Correlation between duration of CVS disability and percentage of improvement of CAT and SADQ in TMS group

	Duration of CVS disability "years"		
	r -value	p-value	Sig.
Percentage of improvement of CAT			
Cognitive screen	-0.183	0.513	NS
Spoken language	0.560	0.030	S
Written language	-0.227	0.416	NS
Repetition	-0.220	0.430	NS
Naming	-0.317	0.250	NS
Reading	0.302	0.274	NS
Writing	-0.720	0.002	S
Percentage of improvement of SADQ	-0.165	0.557	NS

DISCUSSION

Post-stroke non-fluent aphasia, a communication disorder characterized by difficulties in speech production and fluency, significantly impacts stroke survivors [16].

rTMS, a non-invasive technique that modulates brain activity using magnetic fields applied to the cortex, emerges as a promising tool for rehabilitation in this population. This study investigated the potential of low-frequency repetitive rTMS to accelerate post-stroke aphasia recovery and improve patients' quality of life. Thirty participants with non-fluent aphasia were equally randomized into TMS and sham groups, ensuring baseline comparability through identical inclusion and exclusion criteria.

Baseline demographics were comparable between the TMS and sham groups. The mean age in the TMS group was 51.80 years (SD ± 14.39, range 28-74 years) and in the sham group was 58.00 years (SD ± 7.60, range 48-70 years). The gender distribution was also similar, with 73.3% male and 26.7% female in the TMS group, and 80.0% male and 20.0% female in the sham group. Statistical analysis confirmed no significant differences in age or gender distribution between the groups.

Our demographic data aligns with previous research. The mean age in our study (51.8-58.0 years) is comparable to **Pedersen *et al.*** [17] who reported a mean age of 64 years in a similar aphasia population. Additionally, the gender distribution in our study reflects findings by **Khedr *et al.*** [18], suggesting aphasia affects both males and females without a significant gender bias.

Occupation distribution (housewives, manual workers, office workers) and residence (rural vs. urban) were also analyzed. No significant differences were found between the TMS and sham groups in terms of either variable ($p > 0.05$). In the TMS group, 53.3% resided in rural areas, while in the sham group, the split was nearly even (46.7% rural, 53.3% urban).

Our findings on occupation distribution (housewives, manual workers, office workers) mirror those of **Armstrong *et al.*** [19], suggesting similar participant profiles across studies.

Additionally, residence (rural vs. urban) distribution did not differ significantly between groups, aligning with **Ribeiro *et al.***[20] who reported no location-based prevalence differences in aphasia.

Notably, all participants were right-handed, consistent with **Waldowski *et al.*** [21] who emphasized the importance of handedness in post-stroke aphasia rehabilitation studies.

To comprehensively assess this spectrum of impairments, the standardized Comprehensive Aphasia Test (CAT) was employed in this study. Our findings suggest that low-frequency rTMS did not significantly improve language performance across groups or assessment time points, as measured by the CAT.

This aligns with studies by **Hong *et al.***[22] **and Waldowski *et al.***[21] who explored the effects of right-hemisphere, low-frequency rTMS on post-stroke aphasia recovery.

Hong *et al.*[22] proposed mechanisms by which low-frequency rTMS might influence language function, their results, similar to ours, did not reveal statistically significant improvements in language abilities following the intervention.

Our findings on the lack of significant language improvement following low-frequency rTMS align with **Waldowski *et al.*** who reported minimal naming improvements across both TMS and sham groups[21].

This suggests that inhibitory rTMS to the right inferior frontal gyrus may not be universally effective for all post-stroke aphasia patients. However, **Khedr *et al.***[18] observed language improvement following dual-hemisphere rTMS with language training in the sub-acute stroke phase.

Discrepancies might be due to several factors. First, our study targeted patients beyond 6 months post-stroke, while **Khedr *et al.*** focused on the sub-acute phase. Second, **Khedr *et al.*** employed a different protocol with dual-hemisphere stimulation and higher frequency stimulation to the affected hemisphere. Additionally, their assessment tool (Hemispheric Stroke Scale) and evaluation timing differed from our CAT assessment conducted immediately after the intervention. Finally, **Khedr *et al.*** incorporated speech/ language therapy, which was absent in our study.

A study **Weiduschat *et al.*** [23] observed significant language improvement following 1 Hz rTMS to the right Broca's homolog in their pilot study, contrasting with our findings. These differences might be due to methodological variations.

Weiduschat *et al.* included a smaller sample and employed the Aachen Aphasia Test, while our study utilized the CAT. Additionally, their intervention involved concomitant speech and language therapy, which was absent in our protocol.

Post-stroke depression (PSD) is characterized by a constellation of symptoms including depressed mood, apathy, changes in appetite and weight, sleep disturbances, fatigue, feelings of worthlessness, and anhedonia (lack of pleasure) [24].

The Stroke Aphasic Depression Questionnaire (SADQ) scores revealed no significant differences in depression severity between the TMS and sham groups before and after the intervention. However, the TMS group exhibited a statistically significant improvement in SADQ scores compared to the sham group, suggesting a potential benefit of rTMS in reducing post-stroke depression.

Our findings demonstrate that rTMS led to significant improvements in SADQ scores within the TMS group, suggesting a positive impact on depression levels.

This aligns with **Khedr *et al.*** [18] and **Rigat** [25] who reported similar benefits of rTMS on post-stroke depression using the SADQ and observed improvements in patient mood and quality of life. These findings suggest that rTMS may offer a promising approach for managing post-stroke depression alongside aphasia rehabilitation.

Conclusion:

The rTMS improved post-stroke depression scores but did not enhance aphasia recovery compared to sham treatment. Further research is needed for rTMS and aphasia. We propose TMS as a promising intervention to improve quality of life and address depression in post-stroke aphasia patients. While TMS may augment traditional speech and language therapy, further investigation is necessary. Studies exploring different parameters, frequencies, stimulation sites, and larger patient cohorts are crucial to optimize TMS efficacy for aphasia rehabilitation. Additionally, future research should elucidate factors contributing to outcome variability. This knowledge will pave the way for personalized TMS protocols tailored to individual patient needs.

Limitation of the study:

The study included small sample size.

Financial and non-financial activities and relations of interest:

None.

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E-ISSN: 2833-3772 | Volume 3 (2024), Issue 5 | Sep-Oct 2024

The Scientific Journal of Medical Scholar

Publisher: Real-Publishers Limited (Realpub LLC)
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