Behavioural Neurology

# Communication, Feeding and Swallowing Disorders in Neurological Diseases

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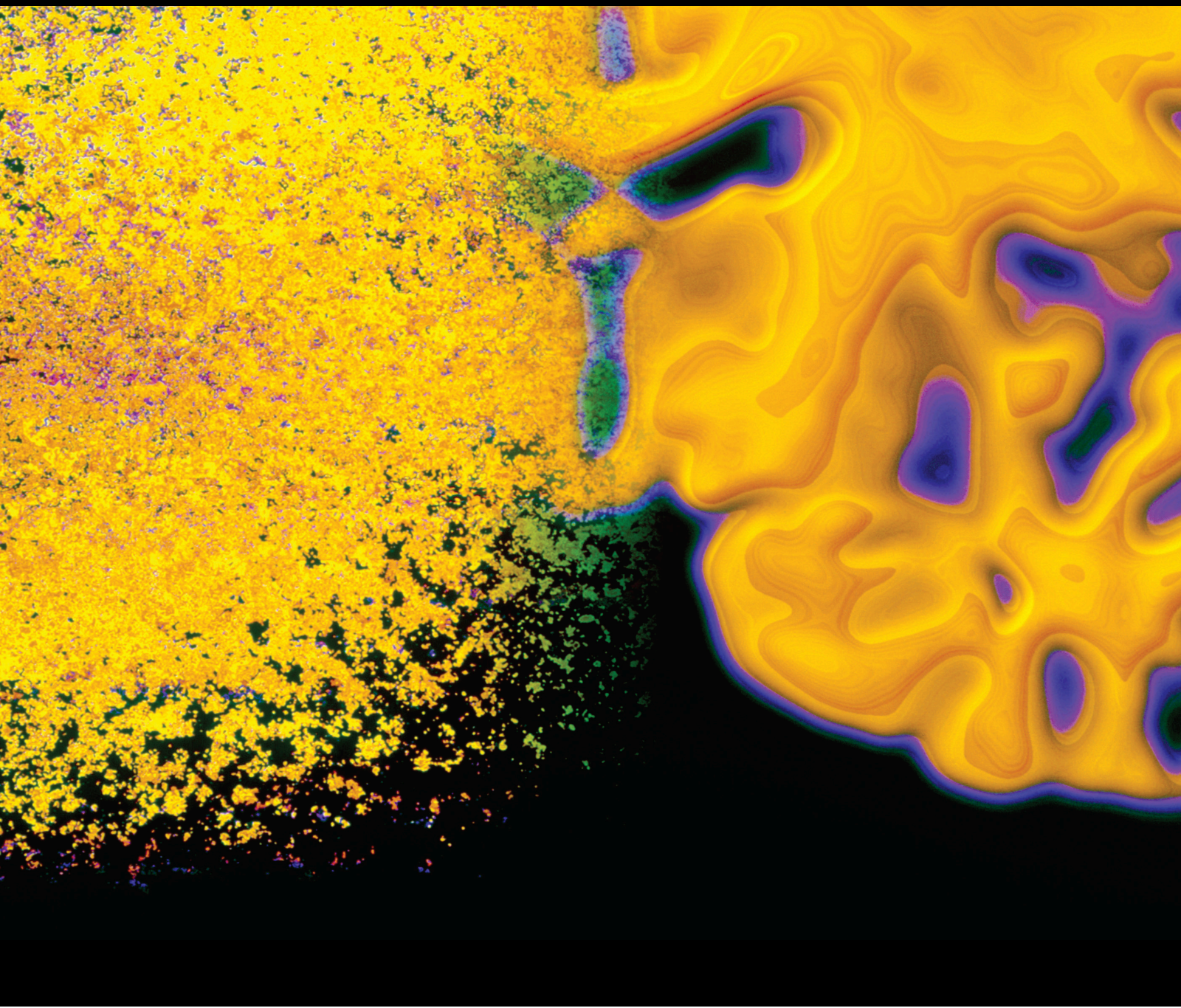
Guest Editors: Lambros Messinis, Efthymios Dardiotis, and Jan Kassubek



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Hindawi
Behavioural Neurology
Volume 2022, Article ID 9851424, 4 pages
https://doi.org/10.1155/2022/9851424

*Editorial*

# Communication, Feeding and Swallowing Disorders in Neurological Diseases

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Received 18 March 2022; Accepted 18 March 2022; Published 21 April 2022



The multifaceted clinical conditions due to neurological diseases seriously burden patients, their families, and caregivers with disabilities and handicaps, including communication and eating-swallowing disorders which are difficult to cope with and have both a high prevalence and substantial impact on quality of life (QoL). Although these deficits affect millions of patients all over the world, their impact and management has not yet been fully investigated and appreciated in clinical settings. This underestimation of communication and eating-swallowing disorders in neurological diseases led us to organize the current special issue. Our aim was to collect relevant studies from international scientific groups and to provoke a discussion about the unmet needs of many sufferers and the heavy duty of scientists working mainly in clinical settings responsible for their management and relief.

Cerebrovascular diseases represent one of the most common causes of morbidity and mortality worldwide [1]. Although in recent years the rates of stroke in wealthy countries have declined, it has increased to double figures in underdeveloped countries, in which, furthermore, the rates of stroke-related disability and mortality are at least 10 times higher [2]. Among the consequences of stroke, aphasia is one of the most devastating, but also frequent sequelae, present in 21-38% of acute stroke patients and associated with worse outcome and expenditure [3, 4]. On the other hand, poststroke dysphagia, although very common and highly correlated with medical complications, such as aspiration pneumonia, is often difficult to be detected, prevented, and treated, especially in clinical settings without specialized personnel [5–7].

Traumatic brain injuries (TBI) represent a common cause of death and disability (the most common among young adults in developed countries) [8]. Cognitive impairment is frequent and disabling, and depending on its severity, usually a long-term consequence of TBI, responsible for the reduced quality of life and difficulties in many aspects of everyday functioning [9]. Oropharyngeal dysphagia is also common in TBI patients, being reported in almost one-third, 27-30%, of patients [10].

These disorders are also very demanding for people living with progressive neurodegenerative diseases, since functional communication and the ability of self-feeding are globally affected, and their maintenance is highly challenging. Different disorders of language and communication are associated with different forms of dementia, forming distinct clinical profiles and expanding from onset and through the entire course of the underlying diseases, and their evaluation can inform and improve clinical judgments, diagnostically and therapeutically [11]. They include aphasia, apraxia of speech, dysprosodia, alterations in facial expression and gestures, and dysarthria and are present, even early, in most types of dementia [11, 12]. Additionally various eating and swallowing disorders occur in all dementias, such as decrease or increase of appetite, metabolic dysregulation, changes in eating habits, eating apraxia, agnosia of food,

and swallowing difficulties [10, 13]. These features appear in the totality of sufferers, during the disease course, and dramatically affect these people's lives [13]. It is of specific concern that many of these disorders share common neural pathways and mechanisms and can occur simultaneously in the same patient.

Cognitive disorders, mainly affecting executive functions, memory, and attention systems, and emotions interfere with functional communication and food consumption, forming a complex and therapeutically challenging landscape [14]. Despite the significant impact of these disorders, in many countries and perhaps most clinical settings, their screening, assessment, diagnosis, and management are not a routine clinical practice yet. The consequences are suboptimal care, earlier loss of independence, reduced quality of life, additional load and costs for care givers, unnecessary gastrointestinal tubing, and serious complications.

With pharmaceutical remedies for the management of such disorders in acquired brain injuries still absent, the importance of cognitive rehabilitation and multidisciplinary approaches, including, but not limited to, neurologists, clinical neuropsychologists, neuro-radiologists, ENT, and specialized speech-language pathologists, was highlighted by us, in a dedicated special issue hosted in this journal [15].

In the current special issue, we host six novel articles from international groups of colleagues. Four of them are clinical studies, one case report, and one review article.

A. M. Georgiou and M. Kambanaros investigated the effectiveness of two different transcranial magnetic stimulation (TMS) paradigms as treatment options for recovery of language deficits in six persons living with chronic poststroke aphasia, in addition to speech and language therapy. Both paradigms used inhibitory stimulation trajectories, targeting the contralesional hemisphere, and more specifically the right pars Triangularis. Three of them were treated with low frequency, 1 Hz, repetitive TMS, and the remaining three were treated with high frequency, continuous theta burst stimulation. When language abilities and QoL were assessed at baseline, immediately after and two months posttreatment, all subjects showed "trends towards improvement" in several language skills, while the rated QoL showed mixed results. One subject followed for two years sustained the treatment-mediated improvement in comprehension and reading skills over time. The authors discuss possible mechanisms of action of their approach, concluding that inhibitory TMS has the potential to drive neuroplastic changes that facilitate language recovery in their sample.

From the same department, D. Kranou-Economidou and M. Kambanaros presented an instructive case study of a 63-year-old male with poststroke aphasia whose working memory (WM) impairment was targeted by the application of intermittent theta burst stimulation (iTBS) combined with computerized WM training to improve receptive and expressive language skills, and through this, communication efficiency and QoL. The treatment program involved iTBS application to the left dorsolateral prefrontal cortex (DLPFC), an area responsible for WM, for 10 consecutive sessions. The participant received a 3-minute iTBS application followed by 30-minute computer-assisted WM training. Treatment beneficially effected naming, reading, WM, reasoning, narrative, communication efficiency, and QoL. Even though this effectiveness was shown in a single case, the implication of cognitive rehabilitation and TMS, in a subject with poststroke aphasia, traditionally treated only with speech and language therapy, evokes discussion about new horizons in aphasia management.

S. Xu et al. addressed the exciting issue of the association and correlation of recovery of poststroke aphasia (PSA) with upper extremity (UE) motor dysfunction, in other words, whether the presence of PSA affects UE motor performance, and if language function associates with UE motor performance. In this multicenter, cross-sectional study, the UE motor status of 435 stroke patients was compared and correlated with the occurrence of PSA in three periods (1-3 months, 4-6 months, and >6 months). Fugl-Meyer assessment for the upper extremity and action research and arm test were used to evaluate the UE motor status, while Western Aphasia Battery-Aphasia Quotient and Boston Diagnostic Aphasia Examination were used to assess the presence, type, and severity of aphasia. The authors concluded that stroke patients with PSA had worse UE motor performance, while UE motor status and language function showed positive correlations, in which spontaneous speech ability significantly accounted for the associations.

Y. Yu et al. set the question about the relationship between alcohol consumption and cognitive impairment after ischemic stroke, investigating the associations of aldehyde dehydrogenase 2 (*ALDH2*) polymorphisms and alcohol consumption with cognitive impairment in 180 Han Chinese ischemic stroke patients from four community health centers in Bengbu, China. Cognitive status was screened in these patients by using the Montreal Cognitive Assessment (MoCA), and *ALDH2* genotypes were determined using polymerase chain reaction and direct sequencing. The results showed that *ALDH2* polymorphisms (and more specifically, the *ALDH2* $*$ *2* mutant allele) and higher alcohol consumption had a significant synergistic effect on cognitive impairment and swallowing ability after ischemic stroke, indicating that it may be a useful biomarker for cognitive rehabilitation following ischemic stroke. The authors, furthermore, suggested that *ALDH2* might be involved in the pathogenesis and progression of cognitive impairment after ischemic stroke, as well as having a role in alcohol metabolism.

Regarding feeding disorders and other patient populations, our colleagues M. E. Widman-Valencia et al. studied the relationship between oral motor treatment and the improvement of abilities for feeding and swallowing in boys and girls with cerebral palsy (CP), the most common cause of severe physical disability and motor function deterioration in children. Thirty children between 3 and 14 years old, residing in the state of Yucatán, Mexico, with a diagnosis of CP (predominant diagnosis was spastic CP and tetraplegia), with gross motor function levels from II to V, of whom 50% received oral motor treatment, were included in the study. Results showed significant improvement in mandibular mobility, tongue activity, abnormal reflexes, control of breathing, and general oral motor skills, for those treated, regardless of the severity of gross motor

involvement. On the contrary, within the sample that did not receive oral motor treatment, 46% presented low or very low weight, and 40% referred recurrent respiratory diseases. It was concluded that feeding skills significantly improve with treatment. Furthermore, oral motor treatment was associated with a lower presence of respiratory diseases and nutritional compromise.

Finally, C. Petsani and colleagues reviewed the literature on available studies about the efficacy of rTMS in the treatment of different neurodegenerative parkinsonian disorders, namely, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), and dementia with Lewy bodies (LBD). These syndromes present with heterogeneous clinical phenotypes, reflecting different underlying pathophysiological mechanisms, being either "synucleinopathies" or "tauopathies," and are characterized by a variety of motor and nonmotor signs and a lack of disease modifying therapies. For PSP patients, cerebellar rTMS holds promise in tackling postural stability and speech impairment, while rTMS over the motor areas could perhaps also be beneficial for their motor symptoms and LF-rTMS over the right DLPFC for resistant major depression. For MSA patients, targeting the left primary motor cortex (M1) with high frequency (HF) rTMS could have a significant improvement on motor dysfunction, while rTMS over the cerebellum, acting on the abnormal cerebellar-cortical inhibitory neuronal connections, could also prove beneficial. For CBD and LBD, there are still very limited data. Overall, research is still at a preliminary phase, with large, double-blind studies lacking in the literature.

From the contributing articles in this special issue, only a limited proportion of the wide range of communication and feeding disorders that constitute part of the clinical entity of many neurological disorders is presented. Still, we hope that the special issue provides an increased awareness on this topic and the significance of ongoing research related to the combinations of therapies in the associated conditions. The articles may assist clinicians when formulating evidence-based neurorehabilitative interventions and further highlight the necessity of multidisciplinary action and collaboration. However, the need for large-scale multidisciplinary and multisite studies to target the clinical presentation and cooccurrence of communication and eating disorders (e.g., dysarthria and dysphagia in parkinsonian syndromes, multiple sclerosis, or stroke), screening and evaluation tools for assessment of these conditions, and combined neurobehavioral, neuromodulational, and pharmacological interventions for the management of communication and feeding/eating disorders remain a priority.

## Conflicts of Interest

The authors report no conflict of interest or private agreements with companies concerning the manuscripts in this Special Issue.

## Acknowledgments

We are deeply grateful to all authors who contributed their valuable articles and expert reviewers for their significant contribution. We would also like to thank the journal for hosting and assisting in all aspects to make this special issue possible.

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*Lambros Messinis*
*Efthimios Dardiotis*
*Jan Kassubek*

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Hindawi
Behavioural Neurology
Volume 2022, Article ID 7274115, 25 pages
https://doi.org/10.1155/2022/7274115

*Research Article*

# The Effectiveness of Transcranial Magnetic Stimulation (TMS) Paradigms as Treatment Options for Recovery of Language Deficits in Chronic Poststroke Aphasia

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Received 12 April 2021; Accepted 18 December 2021; Published 11 January 2022

Academic Editor: Efthymios Dardiotis



*Background*. In an effort to boost aphasia recovery, modern rehabilitation, in addition to speech and language therapy (SALT), is increasingly incorporating noninvasive methods of brain stimulation. The present study is aimed at investigating the effectiveness of two paradigms of neuronavigated repetitive transcranial magnetic stimulation (rTMS): (i) 1 Hz rTMS and (ii) continuous theta burst stimulation (cTBS) each as a standalone treatment for chronic aphasia poststroke. *Methods*. A single subject experimental design (SSED) trial was carried out in which six people with aphasia (PWA) were recruited, following a single left hemispheric stroke more than six months prior to the study. Three individuals were treated with 1 Hz rTMS, and the remaining three were treated with cTBS. In all cases, TMS was applied over the right pars triangularis (pTr). Language assessment, with standardized and functional measures, and cognitive evaluations were carried out at four time points: twice prior to treatment (baseline), one day immediately posttreatment, and at follow-up two months after treatment was terminated. Quality of life (QoL) was also assessed at baseline and two months posttreatment. In addition, one of the participants with severe global aphasia was followed up again one and two years posttherapy. *Results*. For all participants, both rTMS paradigms (1 Hz rTMS and cTBS) generated trends towards improvement in several language skills (i.e., verbal receptive language, expressive language, and naming and reading) one day after treatment and/or two months after therapy. Rated QoL remained stable in three individuals, but for the other three, the communication scores of the QoL were reduced, while two of them also showed a decline in the psychological scores. The participant that was treated with cTBS and followed for up to two years showed that the significant improvement she had initially exhibited in comprehension and reading skills two months after TMS (1st follow-up) was sustained for at least up to two years. *Conclusion*. From the current findings, it is suggested that inhibitory TMS over the right pTr has the potential to drive neuroplastic changes as a standalone treatment that facilitates language recovery in poststroke aphasia.

## 1. Introduction

To boost poststroke aphasia rehabilitation further, several noninvasive brain stimulation (NIBS) techniques have been applied to poststroke aphasia individuals over the past 20 years with promising results. Two of the most common methods that are being investigated are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). The rationale behind their application is that both methods modulate neuronal plasticity and, in this way, facilitate language recovery.

Transcranial magnetic stimulation has shown exploratory potential to induce language recovery in aphasia poststroke [1]. Before 2014, only a few rTMS studies on poststroke aphasia recruited sufficiently large numbers of participants [2]. The majority of those studies explored the effects of low-frequency (LF) TMS over the contralesional inferior frontal gyrus (IFG) followed by speech and language

therapy (SALT) in a clinically heterogeneous group of people with aphasia (PWA) at the postacute phase of recovery [3–6] with mixed results; hence, no conclusions could be drawn regarding the efficacy of LF rTMS over the contralesional IFG on recovery of poststroke aphasia [2]. After 2014, additional research with larger numbers of PWA has offered further insight on the possible effectiveness of rTMS on aphasia recovery in subacute aphasia [7, 8] and in the chronic stage [9–11]. The potential positive outcomes of rTMS on aphasia recovery poststroke have been further investigated by trials applying short rTMS burst protocols (e.g., theta burst stimulation (TBS)) with promising results [12–16]. For a review of TBS, see Huang and Rothwell [17] and Huang et al. [18]. Collective findings from LF rTMS in poststroke aphasia suggest that LF rTMS over the right IFG has the potential to reorganize the language networks and drive language improvement in people with poststroke aphasia. Nevertheless, with regard to high-frequency (HF) TMS, according to a recent review [2], no recommendations can be made for its use in poststroke aphasia rehabilitation.

Research on TMS aphasia rehabilitation is ongoing and promising but remains inconclusive for several reasons. For example, there are many inconsistencies between studies in several domains such as the following: (i) number of participants, (ii) paradigms employed (inhibitory vs. excitatory rTMS and inhibitory together with excitatory rTMS), (iii) anatomical sites of stimulation, (iv) methods of localization of stimulation sites (e.g., 10-20 international system vs. frameless stereotactic neuronavigation systems), (v) type and intensity of SALT, and (vi) the use of reliable outcome measures. With regard to SALT that is used as adjuvant to TMS, there are several studies that highlight major inconsistencies in SALT types and intensities. Examples of relevant randomized controlled trials include a study [7] in which a 45-minute SALT program was applied according to best-practice guidelines [19], a trial [20] in which a 30-minute SALT program focusing on language comprehension and expression was followed, a study [21] that used a 30-minute SALT regimen focusing on naming, another study [8] that applied a 45-minute SALT program aimed at reactivation of word retrieval, another trial [11] that used a 60-minute SALT program twice a week emphasising verbal expressive skills, five trials that followed a 45-minute SALT program focused on patient-specific language problems [3–5, 22, 23], and a study [6] that applied a 45-minute program focusing on expression and comprehension of spoken language. The wide variability in the reported studies and the absence of standardization of the SALT programs question their efficacy by not allowing the disentanglement of the beneficial effects of TMS from those of SALT. Therefore, the extent of the improvement on language abilities attributed to TMS cannot be evaluated.

The present study is aimed at measuring the effectiveness of rTMS as a standalone treatment for chronic stroke-induced aphasia. The objectives of the study were as follows:

(i) To explore whether continuous 1 Hz rTMS and cTBS (independent variables, IV) could modify performance on language tests (dependent variables, DV) one day (short-term) and/or two months (long-term) posttreatment when administered for 10 consecutive days over the right pars triangularis (pTr) of individuals with chronic aphasia

(ii) To explore whether the above protocols (i.e., cTBS and 1 Hz rTMS) could bring about similar changes in language performance in the cohort of PWA under investigation

## 2. Materials and Methods

*2.1. Bioethics Approval.* Ethical approval for this study was obtained from the Cyprus National Bioethics Committee (CNBC) (EEBK/ΕΠ/2017/37).

*2.2. Participants.* A single-subject experimental design (SSED) trial was undertaken at the University Rehabilitation Clinic of the Department of Rehabilitation Sciences at the Cyprus University of Technology (CUT). Adults who had suffered a single left hemisphere stroke at least six months prior to participating in the study were actively sought for recruitment. The recruitment phase was open for 15 months. The inclusion criteria were as follows: (1) aged between 18 and 75 years of age, (2) native speakers of (Cypriot) Greek, (3) right-handed, (4) a diagnosis of a first ever left-sided middle cerebral artery (MCA) stroke verified by magnetic resonance imaging (MRI) or computerized tomography (CT), (5) chronic aphasia stage (>6 months poststroke), (6) no history of dementia or other neurological illnesses, and (7) no current participation in any type of language rehabilitation. Exclusion criteria included the following: (1) Greek not the mother tongue; (2) left-handedness; (3) prior stroke(s); (4) MRI and TMS exclusion criteria; (5) severe dysarthria affecting intelligibility; (6) any other neurological condition affecting the sensorimotor system (e.g., brain tumour); (7) medication that alerts brain excitability to avoid pharmacological influences on TMS, as there is evidence that the extent and direction of NIBS-induced plasticity can be significantly modulated by many neuropharmacological agents [24]; (8) cognitive disorders known before the stroke; and (9) involvement in behavioral language rehabilitation. Overall, 20 people were recruited but only eight actively took part and completed all phases of the study. Two participants were recruited to the pilot study (see [25]) and the remaining six to the main study (see Table 1 for demographics and clinical characteristics of the six participants and Figure 1 for brain MRIs). The remaining seven individuals from the initial cohort did not participate due to caregivers' reluctance/refusal because of time commitment to the study, and three PWA withdrew from the study during the TMS treatment stage while two more withdrew because of claustrophobia and subsequent failure to undergo an MRI scan.

*2.3. Study Eligibility Measures.* To determine eligibility for the study the following measures were carried out: (1) a detailed case history on demographics and health status, (2) a screening checklist for TMS eligibility, (3) the Hemispatial Neglect Test [26], and (4) the Handedness Inventory

Table 1: Demographics and clinical characteristics of the participants.

| Participant | Sex | Age (years) | Handedness | Education (years) | Type of stroke | Months post stroke | Lesion site (left hemisphere) | Type of aphasia | Severity of aphasia | SALT prior to enrolment | Termination of SALT |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 74 | Right | 6 | Ischemic | 48 | Diffuse frontal, parietal, and temporal (middle and superior gyri) lobes; insula; basal ganglia | Global | Severe | 20 months–2 times per week–45 min of SALT | 2 years before enrolment |
| 2 | M | 61 | Right | 12 | Ischemic | 9 | Broca's and Wernicke's areas; arcuate fasciculus; insula; inferior precentral gyrus; temporal pole | Anomic | Moderate-severe | 6 months–2 times per week–45 min of SALT | 2 months before enrolment |
| 3 | M | 48 | Right | 15 | Ischemic | 11 | IFG; internal capsule; insula; caudate nucleus; putamen; inferior precentral gyrus | Broca's | Moderate-severe | 8 months–4 times per week–45 minutes | 10 days before enrolment |
| 4 | F | 72 | Right | 12 | Ischemic | 50 | Broca's and Wernicke's areas; arcuate fasciculus; insula; superior posterior temporal gyrus; middle posterior temporal gyrus | Anomic | Moderate-severe | 24 months–2 times per week–45 min of SALT | 2 years before enrolment |
| 5 | M | 55 | Right | 17 | Ischemic | 8 | Precentral gyrus; postcentral gyrus; arcuate fasciculus; internal capsule; caudate nucleus; putamen | Global | Severe | 4 months–4 times per week–45 minutes | 10 days before enrolment |
| 6 | M | 26 | Right | 16 | Ischemic | 109 | IFG; MFG; SFG; insula; basal ganglia; arcuate fasciculus; internal capsule; anterior temporal lobe; Wernicke's area, anterior temporal lobe most likely due to an arachnoid cyst | Anomic | Mild | 10 months–4 times per week–45 minutes | 7 years before enrolment |

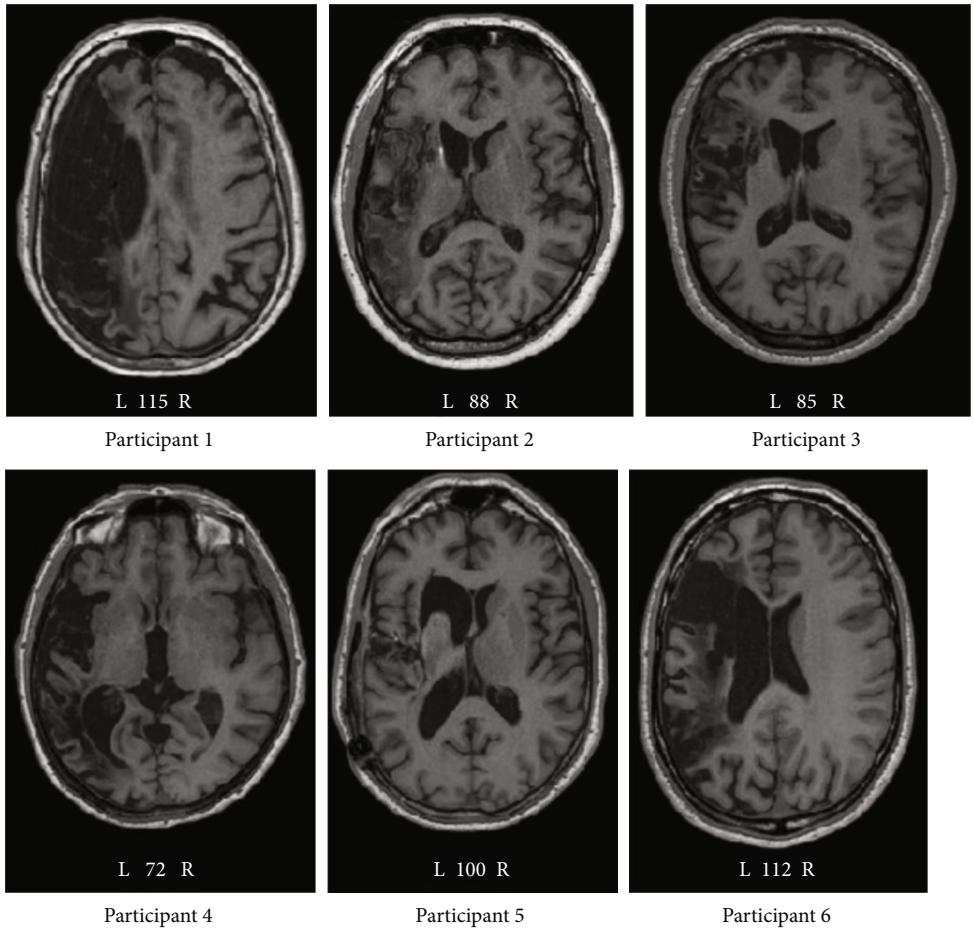



Figure 1: Brain MRI scans (axial plane) of the participants. Key: L: left hemisphere; R: right hemisphere; numbers indicate serial axial slice images.

(Edinburgh Handedness Inventory—Short Form [27]) to determine handedness.

### 2.4. Cognitive-Linguistic Measures Performed at Baseline, Posttreatment, and Follow-Up

*2.4.1. The Greek Boston Diagnostic Aphasia Examination-Shortened Version (BDAE-SF).* The Greek BDAE-SF [28] was used for language examination (i.e., oral and written language comprehension, expressive language, reading, and writing).

*2.4.2. The Peabody Picture Vocabulary Test–Revised (PPVT-R).* The short form (32 stimuli) of the Greek PPVT-R [29] was used to measure single word receptive vocabulary. The full and short versions of the PPVT-R are equivalent and constitute reliable and valid assessment tools of vocabulary for Greek students and immigrants who speak Greek [29].

*2.4.3. The Greek Object and Action Test (GOAT).* The Greek Object and Action Test (GOAT) is used to assess naming of nouns and verbs for assessment and/or research purposes in Greek speakers. It contains 84 coloured photographs measuring 42 actions and 42 objects. The test in total (production and comprehension subtests) takes under an hour to administer. The GOAT is reported in published studies investigating verb-noun grammatical dissociations across language-impaired populations [30]. For the purposes of this study, 19 informative verbs were used that distinguish language impaired from nonimpaired groups. This informative version was produced based on a new algorithm (ALNOVE) proposed to dismiss redundant/noninformative items from the tool [31].

*2.4.4. The Multilingual Assessment Instrument for Narratives (MAIN).* The Greek version of the Multilingual Assessment Instrument for Narratives (MAIN) [32] was used to evaluate production of narrative skills at the macro- and microstructure levels. In this study, the "Baby Goats" story, a story similar in concept to an Aesop fable, making it suitable for adult populations, was used.

*2.4.5. The Raven's Coloured Progressive Matrices (RCPMs).* The 36-item Raven's Coloured Progressive Matrix (RCPM) [33] was applied for problem-solving ability examination.

### 2.5. Quality of Life Measure: Used at Baseline and at Follow-Up

*2.5.1. Stroke and Aphasia Quality of Life Scale-39 Item (SAQOL-39).* The Greek version of the Stroke and Aphasia Quality of Life scale-39 item (SAQOL-39) [34] was applied for the assessment of TMS effects on QoL. The Greek

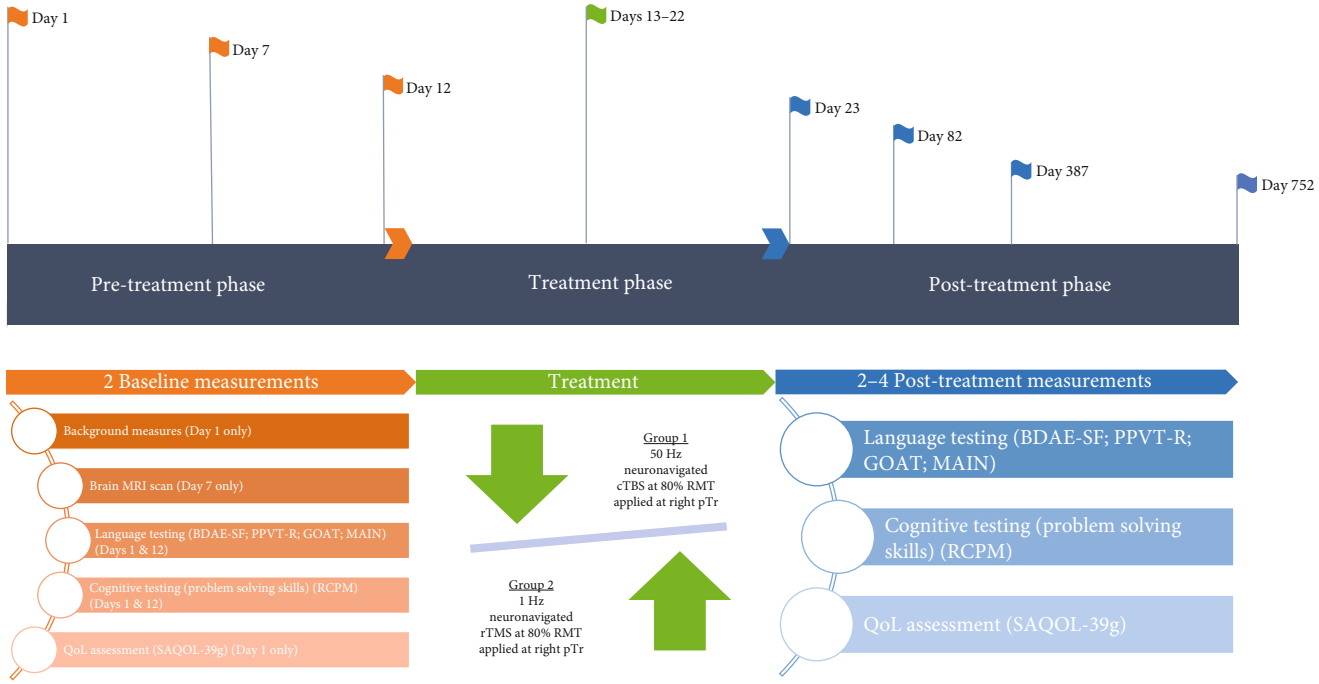



Figure 2: Experimental timeline of the study.

generic SAQOL-39 (SAQOL-39g) (i.e., the tool used in stroke patients without aphasia) is valid and reliable [35] and was used, and QoL was assessed using proxy ratings (caregivers) with all participants as three participants (P1, P4, and P5) struggled to respond to complex questions due to comprehension deficits.

*2.6. Linguistic, Cognitive, and QoL Assessment and Analysis Procedures.* All participants were assessed twice at baseline, one day posttreatment, and at two-month follow-up on all cognitive-linguistic measures. One participant (P1) was further assessed one and two years posttreatment. A schematic diagram illustrating the experimental timeline is shown in Figure 2. All participants did a brain MRI a week before therapy initiation. To ensure treatment fidelity, the Template for Intervention Description and Replication (TIDieR) [36] was used. A speech-language pathologist, blind to the study, performed all assessments and recorded the results in the project database. A second speech-language pathologist, also blind to the study, analyzed the responses. For the analysis of the MAIN, the Quantitative Production Analysis (QPA) protocol [37] as adopted for Greek [38] was applied by a linguist blind to the study protocol.

*2.7. Repetitive TMS (rTMS) Procedures and Protocol.* The six participants were randomly (via a computer-generated randomization schedule) allocated to two groups (three participants in each group) with each group (T1 or T2) receiving only one treatment type. To minimize placebo effects, the participants were informed that they had 50% chance to receive real treatment and 50% chance to receive sham treatment. Therefore, they were blinded to their status of TMS conditioning (real vs. sham) until the end of the study. The treatment procedures that followed are described below.

*2.8. Assessment of Resting Motor Threshold (RMT).* The assessment of rest motor thresholds (RMTs) needed for determination of stimulation intensity was carried out for each participant using surface electromyography (EMG) [39]. After locating the "hot spot," for the appropriate RMT of the FDI, the standard stimulus magnitude used for mapping of the FDI was used and then the stimulus intensity was progressively reduced in 2% or 5% steps until the minimum single-pulse stimulator output intensity resulting in motor evoked potentials (MEPs) of at least 50 $\mu$V peak-to-peak amplitude in ≥50% of pursued trials was found. The rate of stimulation was more than 3 secs between consecutive stimuli. Motor threshold levels were used to determine stimulation parameters as they were considered as an indication of cortical excitability.

*2.9. Repetitive TMS (rTMS) Stimulation Parameters.* Participants underwent rTMS at 80% of their individual RMT, using the Magstim Rapid2® stimulator (Magstim Co., Wales, UK) connected to a 70 mm Double Air Film Coil. Stimulation parameters were in accordance with published guidelines [40]. The position of the coil was guided by a frameless stereotactic neuronavigation system (ANT NEURO) that uses the individual patients' MRI scan to precisely localize the target area for stimulation. Before stimulation, a T1-weighted MRI image was obtained from each patient to locate the optimal coil position.

*2.9.1. Group T1: Continuous Theta Burst Stimulation (cTBS) over the Right Pars Triangularis (pTr).* Participants in this

group (P1, P2, and P3) received inhibitory rTMS (continuous theta burst stimulation paradigm, cTBS) to the pTr in the right inferior frontal gyrus (homologous BA45), following a published protocol [18].

*2.9.2. Group T2: 1 Hz (Low Frequency) rTMS over the Right Pars Triangularis (pTr).* Participants in this group (P4, P5, and P6) received 10 daily stimulation treatments of 1 Hz rTMS (1200 pulses in 20 minutes each) over the right pTr.

*2.10. Statistical Analyses.* To analyze data with categorical outcomes (e.g., correct/incorrect and target word naming), Weighted Statistics (WEST) ("West-Trend" and "West-ROC" (one tailed)) were applied (see [41] for a review and the algorithm that calculated the weighted factors). Such statistics offer a mean of analyzing single-case study data when multiple baselines have been undertaken. Functional language data are reported in detail according to the QPA protocol, and QoL findings are reported rounded to two decimal places.

## 3. Results

*3.1. Categorical Language and Cognitive Outcomes.* The interrater reliability agreement between the two speech and language pathologists who analyzed the data was above 95%. The weights used in this study for the testing schedule of baseline 1, baseline 2, posttreatment (i.e., one day posttreatment), and follow-up (i.e., two months posttreatment) were as follows: (i) −3, −1, 1, and 3 in order to evaluate the trend across the study (WEST-Trend) and (ii) 3, −4, −1, and 2 to compare the rates of change (ROCs) across treatment and no treatment phases (WEST-ROC). This was the main analysis for all participants (P1-P6). However, for participant 1 (P1), the testing schedule was different: baseline 1, baseline 2, posttreatment (i.e., one day posttreatment) follow-up 1 (i.e., two months posttreatment), follow-up 2 (i.e., one year posttreatment), and follow-up 3 (i.e., two years posttreatment). The WEST-Trend and WEST-ROC weights up to follow-up 2 period were −2, −1, 0, 1, and 2 and 2, −2, −1, 0, and 1, respectively. The WEST-Trend and WEST-ROC weights for periods follow-up 1, follow-up 2, and follow-up 3 were −2, 0, and 2 and 1, −2, and 1, respectively. In the last two analyses (up to follow-up 2 and follow-up 3 stages) for P1, WEST-ROC evaluated the rates of change in the short versus long-term periods to explore the possible long-term (i.e., one and two years posttreatment) effects of TMS therapy. Performance on categorical language and cognitive data for all participants is reported in Tables 2 and 3 and Figure 3. Data relating to short-term and long-term effects (up to one-year follow-up) for participant 1 (P1) have been also published previously [42].

*3.1.1. Participant 1 (P1)*

*(1) Short-Term Effects (i.e., One Day Posttreatment) of cTBS (Pre-TMS 1–Pre-TMS 2–Post-TMS).* P1 did not show any overall improvement in comprehension ($t(63) = 0.44$, $p = .32$), problem-solving skills, naming, or reading. However, she showed moderate improvement in expressive language ($t(25) = 1.79$, $p = .04$), but this improvement was not higher in the treated (i.e., TMS period) versus the untreated periods (i.e., baseline periods) ($t(25) = 0.90$, $p = .19$).

*(2) Long-Term Effects (i.e., Two Months Posttreatment) of cTBS (Pre-TMS 2–Post-TMS–Follow-Up 1).* P1 did not show any overall improvement in expressive language ($t(25) = 0.57$, $p = .28$), problem-solving skills, or naming. However, she showed significant improvement in comprehension ($t(63) = 3.66$, $p < .001$) and moderate improvement in reading ($t(28) = 1.79$, $p = .04$), and such improvements were greater during the first follow-up period (i.e., two months post-TMS) compared to the short-term (i.e., one day post-TMS) for both language comprehension ($t(63) = 2.61$, $p < .01$) and reading ($t(28) = 1.79$, $p = .04$).

*(3) Long-Term Effects (i.e., One Year Posttreatment) of cTBS (Post-TMS–Follow-Up 1–Follow-Up 2).* P1 did not improve in expressive language ($t(25) = 0.76$, $p = .75$), cognition, and naming. However, she sustained significant improvement in comprehension ($t(63) = 2.80$, $p = .003$) and moderate improvement in reading ($t(28) = 2.11$, $p = .02$) up to one year post-TMS.

*(4) Long-Term Effects (i.e., Two Years Posttreatment) of cTBS (Follow-Up 1–Follow-Up 2–Follow-Up 3).* P1 did not show any downward trend in cognition ($t(35) = 1$, $p = .16$), expressive language abilities ($t(63) = 0$, $p = .5$), naming, comprehension ($t(63) = 0$, $p = .5$), and reading ($t(28) = -1$, $p = .84$), showing that language gains in comprehension and reading were sustained at least up to two years posttreatment.

*3.1.2. Participant 2 (P2)*

*(1) Short-Term Effects (i.e., One Day Posttreatment) of cTBS (Pre-TMS 1–Pre-TMS 2–Post-TMS).* P2 did not show any overall improvement in either cognition (problem-solving skills) ($t(35) = 0.32$, $p = .37$), comprehension ($t(63) = 1.52$, $p = .07$), expressive language ($t(25) = 0.46$, $p = .32$), or naming ($t(33) = -0.81$, $p = .79$). However, he showed an overall improvement in reading ($t(28) = 1.79$, $p = .04$), but this improvement was not higher in the treated (i.e., TMS period) versus the untreated periods (i.e., baseline periods) ($t(28) = 0.91$, $p = .187$).

*(2) Long-Term Effects (i.e., Two Months Posttreatment) of cTBS (Pre-TMS 2–Post-TMS–Follow-Up 1).* P2 did not show any overall improvement in either cognition (problem-solving skills) ($t(35) = 0.37$, $p = .35$), expressive language ($t(25) = 0.63$, $p = .27$), or reading ($t(28) = 0.81$, $p = .21$). However, he showed an overall improvement in comprehension ($t(63) = 1.76$, $p = .041$) and naming ($t(33) = 1.75$, $p = .04$), but such improvements were not higher during the first follow-up period (i.e., two months post-TMS) compared to short-term (i.e., one day post-TMS) for either comprehension ($t(63) = 0.12$, $p = .45$) or naming ($t(33) = 1.07$, $p = .14$).

*3.1.3. Participant 3 (P3)*

Table 2: Categorical language and cognitive scores at posttreatment and follow-up compared to baseline for P1, P2, and P3.

| Participant item | P1 | | | | | | P2 | | | | P3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | B1 | B2 | P-TMS | F1 | F2 | F3 | B1 | B2 | P-TMS | F1 | B1 | B2 | P-TMS | F1 |
| Problem-solving skills | 7/36 | 8/36 | 8/36 | 8/36 | 7/36 | 7/36 | 27/36 | 30/36 | 28/36 | 32/36 | 35/36 | 34/36 | 33/36 | 35/36 |
| Auditory comprehension | 12/64 | 13/64 | 13/64 | 26/64 | 24/64 | 24/64 | 18/64 | 18/64 | 21/64 | 24/64 | 31/64 | 29/64 | 30/64 | 31/64 |
| Expressive language (Boston naming test—excluded) | 0.5/26 | 0.5/26 | 2/26 | 1/26 | 1/26 | 1/26 | 4/26 | 4/26 | 5/26 | 6/26 | 13.5/26 | 13.5/26 | 13.5/26 | 15/26 |
| Naming—accuracy | 1/34 | 0/34 | 1/34 | 0/34 | 1/34 | 1/34 | 4/34 | 2/34 | 2/34 | 6/34 | 17/34 | 12/34 | 14/34 | 15.5/34 |
| Reading skills | 2/29 | 2/29 | 2/29 | 5/29 | 6/29 | 4/29 | 14/29 | 14/29 | 17/29 | 16/29 | 14/29 | 19/29 | 18/29 | 19/29 |

Key: P1: participant 1; P2: participant 2; P3: participant 3; B1: baseline 1; B2: baseline 2; P-TMS: post-TMS (1 day posttreatment); F1: follow-up 1 (2 months posttreatment); F2: follow-up 2 (1 year posttreatment); F3: follow-up 3 (2 years posttreatment).

Table 3: Categorical language and cognitive scores at posttreatment and follow-up compared to baseline for P4, P5, and P6.

| Participant item | P4 | | | | P5 | | | | P6 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | B1 | B2 | P-TMS | F1 | B1 | B2 | P-TMS | F1 | B1 | B2 | P-TMS | F1 |
| Problem-solving skills | 17/36 | 22/36 | 21/36 | 16/36 | 33/36 | 32/36 | 34/36 | 34/36 | 32/36 | 32/36 | 32/36 | 34/36 |
| Auditory comprehension | 30/64 | 38/64 | 45/64 | 36/64 | 15/64 | 14/64 | 17/64 | 27/64 | 46/64 | 48/64 | 55/64 | 53/64 |
| Expressive language (Boston naming test—excluded) | 16.5/26 | 14.5/26 | 16.5/26 | 12.5/26 | 0/26 | 0/26 | 0/26 | 0/26 | 23.5/26 | 24.5/26 | 24.5/26 | 28.5/26 |
| Naming—accuracy | 4.5/34 | 5/34 | 9/34 | 4.5/34 | 0/34 | 0/34 | 0/34 | 0/34 | 25/34 | 25.5/34 | 25.5/34 | 28.5/34 |
| Reading skills | 23/29 | 21/29 | 23/29 | 25/29 | 8/29 | 9/29 | 11/29 | 9/29 | 24/29 | 26/29 | 28/29 | 27/29 |

Key: P4: participant 4; P5: participant 5; P6: participant 6; B1: baseline 1; B2: baseline 2; P-TMS: post-TMS (1 day posttreatment); F1: follow-up 1 (2 months posttreatment).

*(1) Short-Term Effects (i.e., One Day Posttreatment) of cTBS (Pre-TMS 1–Pre-TMS 2–Post-TMS).* P3 did not show any overall improvement in cognition (problem-solving skills) ($t(35) = -1.43$, $p = .91$), comprehension ($t(63) = 1.13$, $p = .13$), expressive language, or reading ($t(28) = 1$, $p = .17$). However, he showed an overall improvement in naming ($t(33) = 3.01$, $p < .01$), but this improvement was not higher in the treated (i.e., TMS period) versus the untreated periods (i.e., baseline periods) ($t(33) = -.55$, $p = .71$).

*(2) Long-Term Effects (i.e., Two Months Posttreatment) of cTBS (Pre-TMS 2–Post-TMS–Follow-Up 1).* P3 did not show any overall improvement in cognition (problem-solving skills) ($t(35) = 0.57$, $p = .28$), comprehension ($t(63) = 0.33$, $p = .37$), expressive language ($t(25) = 0.33$, $p = .37$), naming ($t(33) = 1.22$, $p < .01$), or reading ($t(28) = 0$, $p = .50$).

### 3.1.4. Participant 4 (P4)

*(1) Short-Term Effects (i.e., One Day Posttreatment) of 1 Hz rTMS (Pre-TMS 1–Pre-TMS 2–Post-TMS).* P4 did not show any overall improvement in cognition (problem-solving skills) ($t(35) = 1.07$, $p = .14$), expressive language ($t(25) = 0$, $p = .50$), or reading ($t(28) = 0$, $p = .50$). However, she showed an overall improvement in comprehension ($t(63) = 3.37$, $p < .001$) and naming ($t(33) = 2.31$, $p = 0.01$), but this improvement was not higher in the treated (i.e., TMS period) versus the untreated periods (i.e., baseline periods) for either comprehension ($t(63) = -.13$, $p = .55$) or naming ($t(25) = 1.09$, $p = .14$).

*(2) Long-Term Effects (i.e., Two Months Posttreatment) of 1 Hz rTMS (Pre-TMS 2–Post-TMS–Follow-Up 1).* P4 did not show any overall improvement in cognition (problem-solving skills) ($t(35) = -2.23$, $p = .98$), comprehension ($t(63) = -.046$, $p = .67$), expressive language ($t(25) = -1$, $p = .83$), naming ($t(33) = -0.29$, $p = .61$), or reading ($t(28) = 1.44$, $p = .08$).

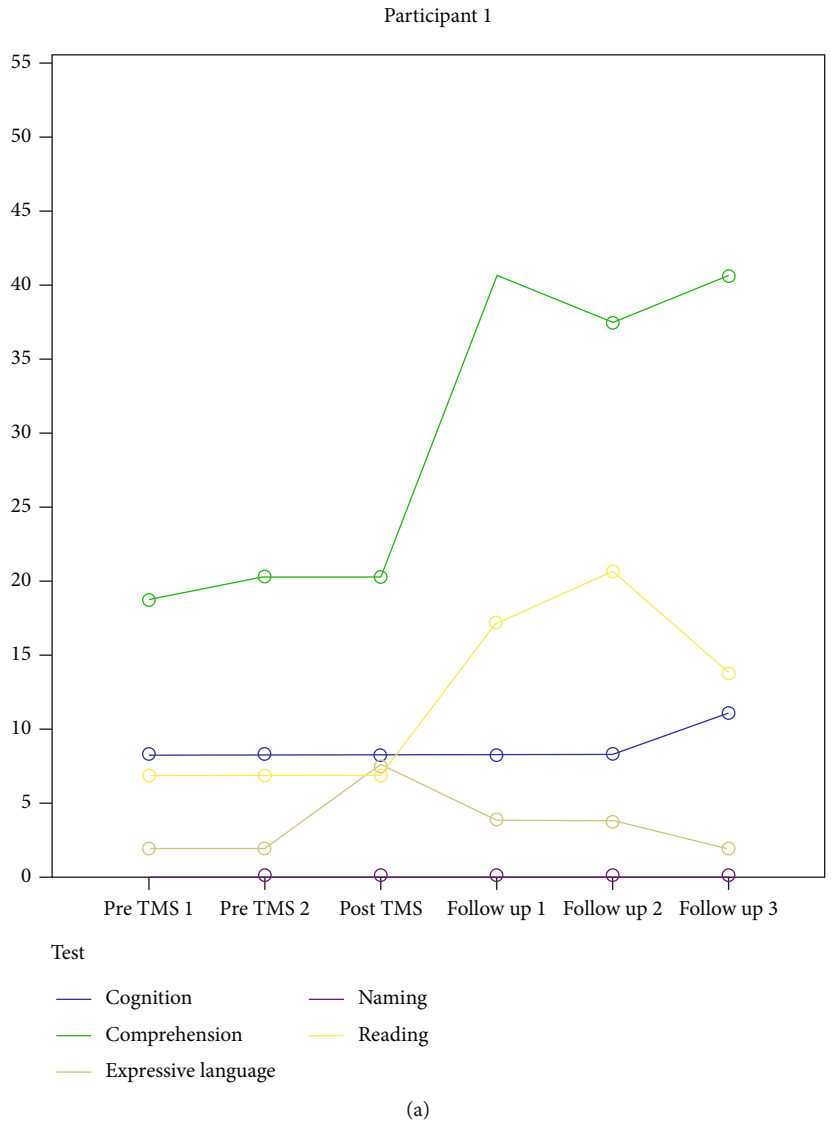
### 3.1.5. Participant 5 (P5)

*(1) Short-Term Effects (i.e., One Day Posttreatment) of 1 Hz rTMS (Pre-TMS 1–Pre-TMS 2–Post-TMS).* P5 did not show any overall improvement in cognition (problem-solving skills) ($t(35) = 0.43$, $p = .33$), comprehension ($t(63) = 0.46$, $p = .32$), expressive language, naming, or reading ($t(28) = 1.36$, $p = .09$).

*(2) Long-Term Effects (i.e., Two Months Posttreatment) of 1 Hz rTMS (Pre-TMS 2–Post-TMS–Follow-Up 1).* P5 did not show any overall improvement in cognition (problem-solving skills) ($t(35) = 1$, $p = .16$), expressive language, naming, or reading ($t(28) = 0$, $p = .50$). However, he showed an overall improvement in comprehension ($t(63) = 2.72$, $p < .01$), but such improvement was not higher during the first follow-up period (i.e., two months post-TMS) compared to short-term (i.e., one day post-TMS) ($t(63) = 1.15$, $p = .12$).

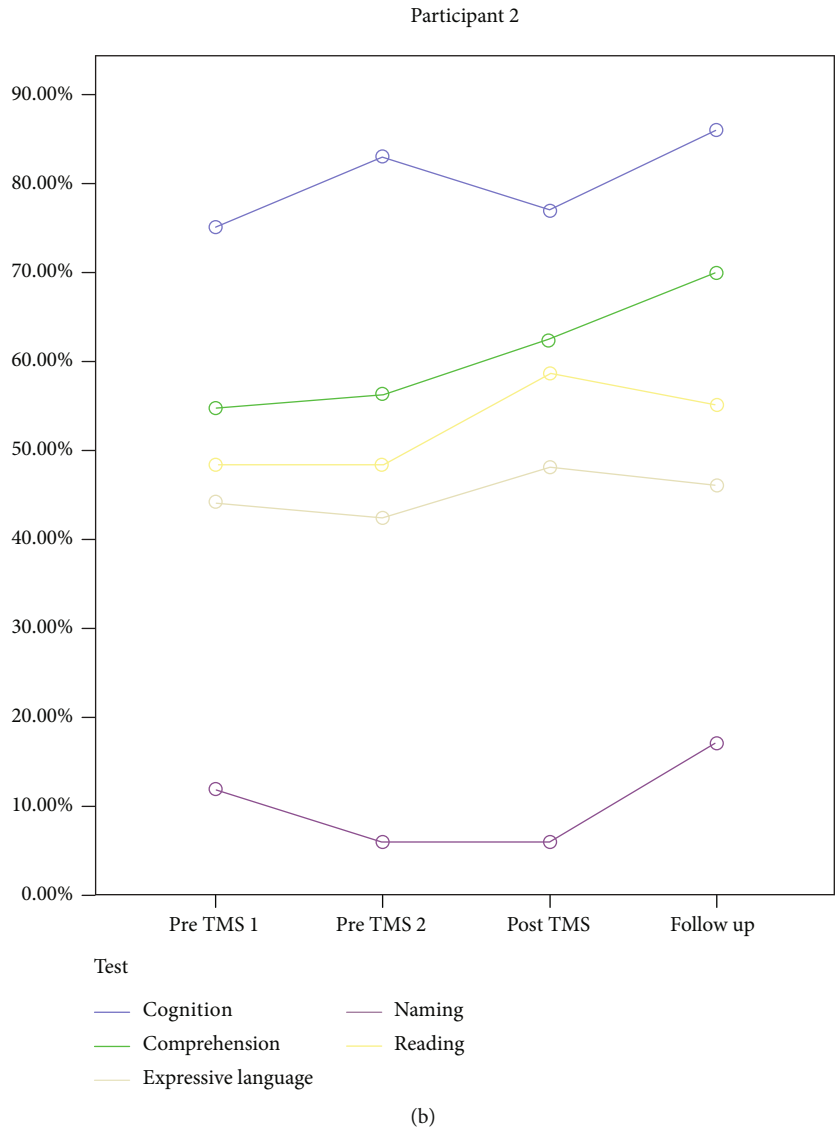
### 3.1.6. Participant 6 (P6)

*(1) Short-Term Effects (i.e., One Day Posttreatment) of 1 Hz rTMS (Pre-TMS 1–Pre-TMS 2–Post-TMS).* P6 did not show any overall improvement in cognition (problem-solving



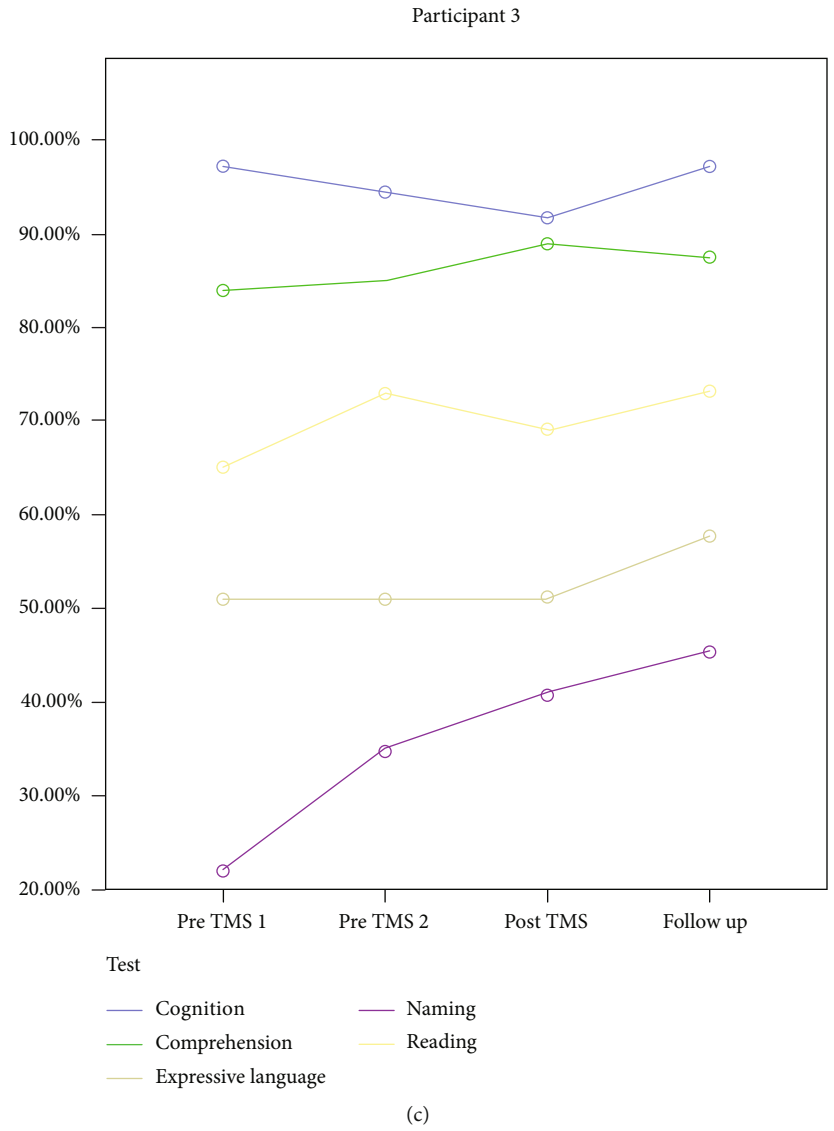

(a)

Figure 3: Continued.



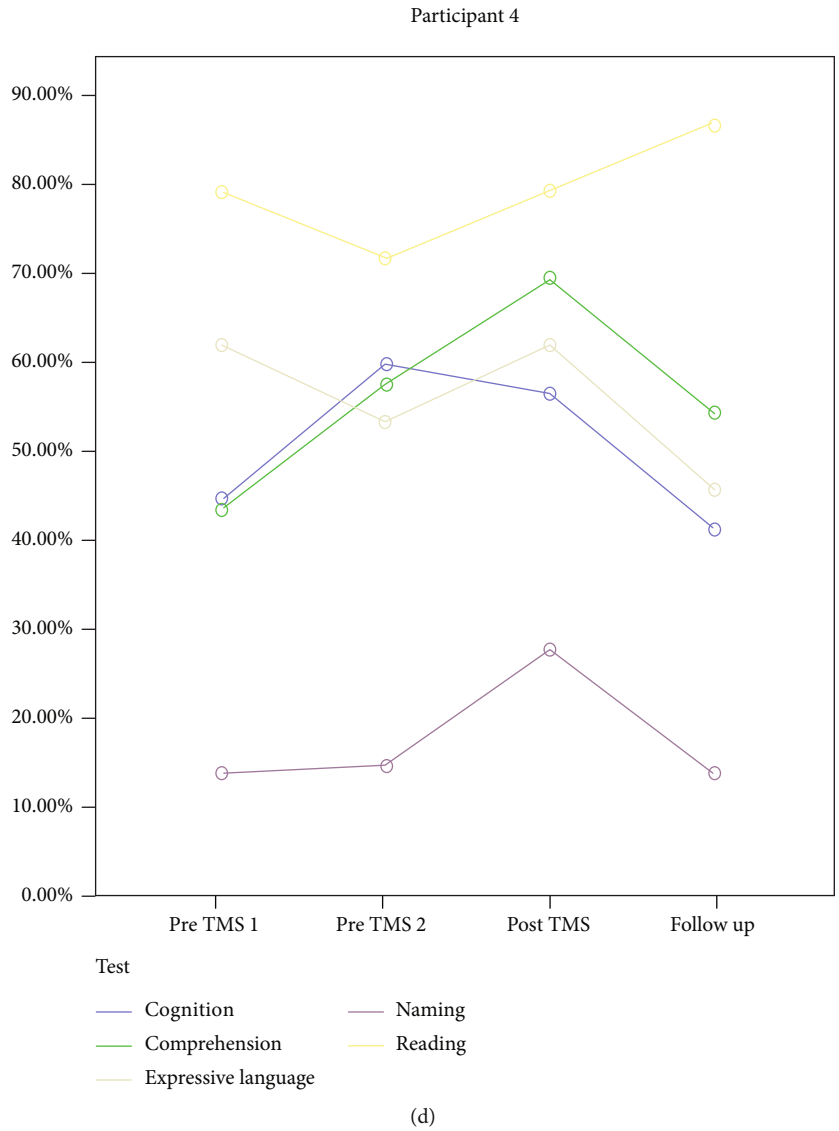

(b)

Figure 3: Continued.



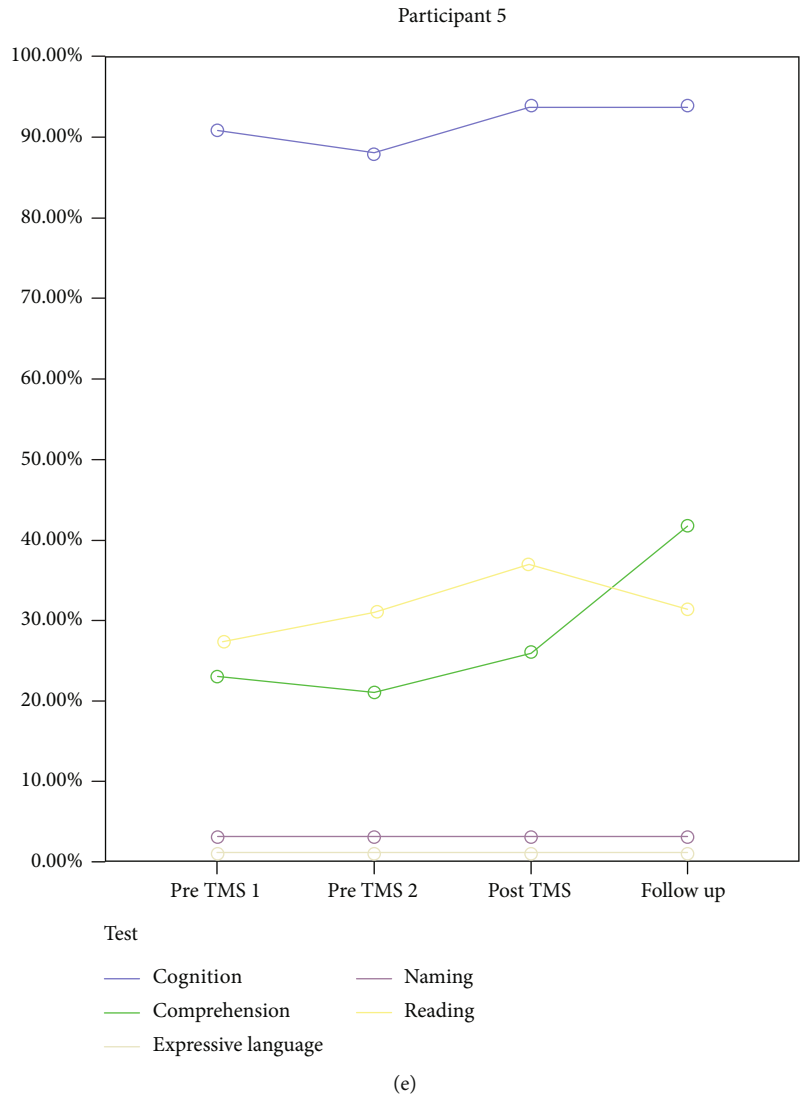

(c)

Figure 3: Continued.




(d)

Figure 3: Continued.




(e)

Figure 3: Continued.

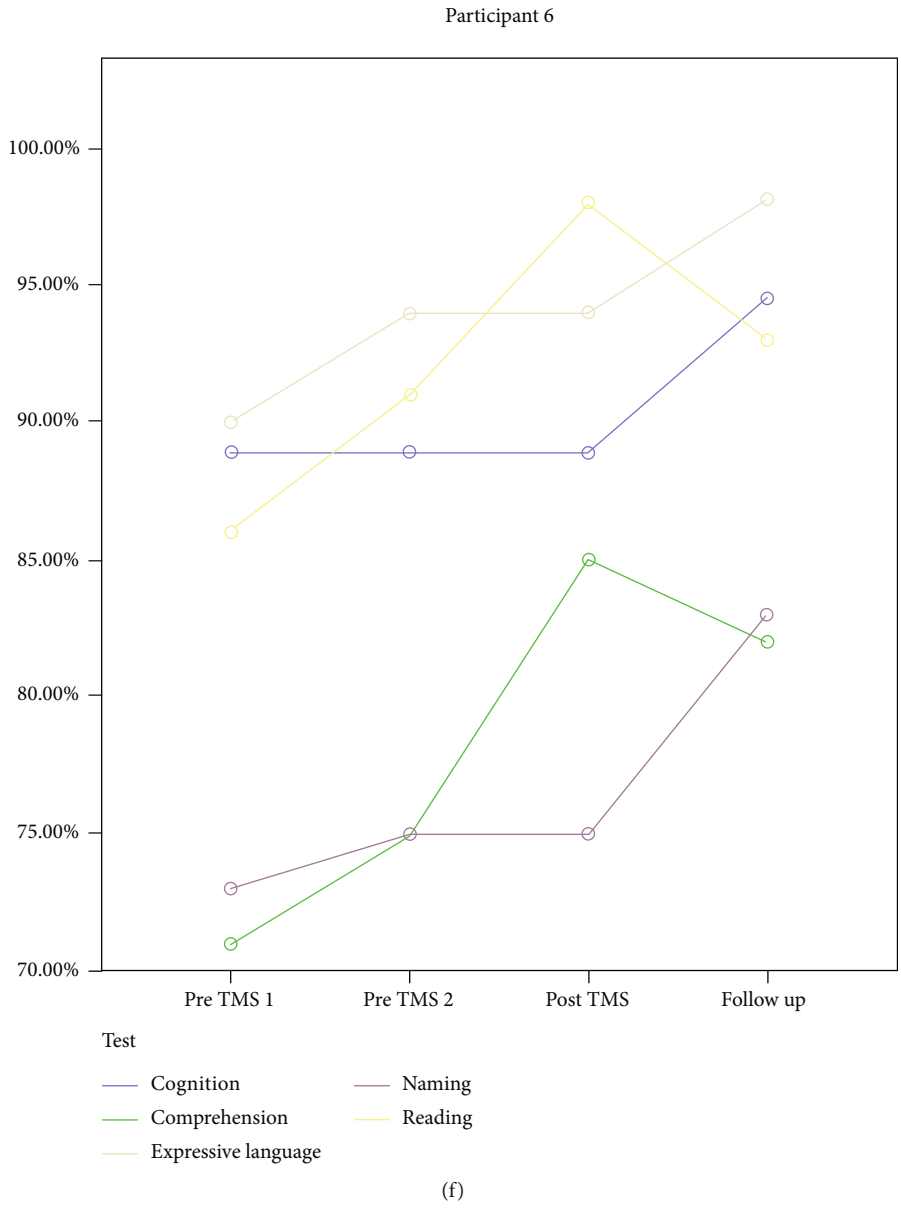



Figure 3: Short-term (one day posttreatment) and long-term (two months, one year, and two years posttreatment) effects of cTBS on cognitive and language performance for all 6 participants. The $Y$ axis depicts relative values to demonstrate the magnitude of variation, if any, between assessments for each domain. Key: pre-TMS 1: baseline 1; pre-TMS 2: baseline 2; post-TMS: 1 day posttreatment; follow-up 1: 2 months posttreatment; follow-up 2: 1 year posttreatment; follow-up 3: 2 years posttreatment; follow-up: 2 months posttreatment.

skills) ($t(35) = 0$, $p = 0.5$), expressive language ($t(25) = 0.70$, $p = .25$), or naming ($t(33) = 0.37$, $p = .35$). However, he showed an overall improvement in comprehension ($t(63) = 2.60$, $p < .001$) and reading ($t(28) = 2.25$, $p = .02$), but such improvements were not higher in the treated (i.e., TMS period) versus the untreated periods (i.e., baseline periods) for either comprehension ($t(63) = 0.77$, $p = .21$) or reading ($t(28) = -0.15$, $p = .44$).

*(2) Long-Term Effects (i.e., Two Months Posttreatment) of 1 Hz rTMS (Pre-TMS 2–Post-TMS–Follow-Up 1).* P6 did not show any overall improvement in cognition (problem-solving skills) ($t(35) = 1$, $p = .16$), expressive language ($t(25) = 1$, $p = .16$), naming ($t(33) = 1.49$, $p = .07$), or reading ($t(28) = .44$, $p = .33$). However, he showed an overall improvement in comprehension ($t(63) = 1.69$, $p = .04$), but such improvement was not higher during the first follow-up period (i.e., two months post-TMS) compared to short-term (i.e., one day post-TMS) ($t(63) = -1.58$, $p = .93$).

*3.2. Functional Language Outcomes.* P1 and P5 had global aphasia and did not produce any narratives. A baseline average score was calculated for each linguistic index for each of the remaining participants (P2, P3, P4, and P6) individually.

But for this study analyses, both baseline measurements were taken into account as they provided information on the range of microstructure performance.

*3.2.1. Participant 2 (P2)*

*(1) Short-Term Outcomes (i.e., One Day Posttreatment).* P2 produced a significantly higher number of narrative words (mostly adverbs and verbs) in the posttreatment assessment phase compared to baseline. Sentence productivity remained stable, and grammatical accuracy remained stable with an exception in the proportion of sentences with verbs that increased. The number and types of errors also remained stable. Results from the short-term microstructure analysis of the MAIN for P2 are shown in Table 4.

*(2) Long-Term Outcomes (i.e., Two Months Posttreatment).* At follow-up, P2 reverted to baseline with regard to the total number of narrative words. This was the case for all lexical categories except pronouns that increased. Sentence productivity also remained stable. With regard to grammatical accuracy, the proportion of sentences with verbs reverted to baseline and well-formed utterances showed a downward trend. The number and types of errors remained stable. Results from the long-term microstructure analysis of the MAIN for P2 are shown in Table 4.

*3.2.2. Participant 3 (P3)*

*(1) Short-Term Outcomes (i.e., One Day Posttreatment).* P3 produced the same number of narrative words in the posttreatment assessment period compared to baseline. Sentence productivity remained stable. Grammatical accuracy also remained stable with the exception of the proportion of well-formed utterances that showed trends for improvement. With regard to error types and numbers, phonological errors and neologism showed a decreasing trend. Results from the short-term microstructure analysis of the MAIN for P3 are shown in Table 5.

*(2) Long-Term Outcomes (i.e., Two Months Posttreatment).* At follow-up, P3 produced more narrative words (closed class words and nouns) compared to baseline. Sentence productivity remained stable, but the embedding index showed a declining trend. With regard to grammatical accuracy, the participant showed trends for improvement in the proportion of sentences with verbs and the proportion of well-formed utterances remained increased compared to baseline. With regard to error types and numbers; the number of phonological errors reverted to baseline, but neologisms retained the downward trend that was also exhibited in the short-term. Overall, the percentage of errors retained the downward trend that was also exhibited in the short-term. Results from the long-term microstructure analysis of the MAIN for P3 are shown in Table 5.

*3.2.3. Participant 4 (P4)*

*(1) Short-Term Outcomes (i.e., One Day Posttreatment).* No differences in the number of narrative words in the short-term were observed with the exception of closed class words that showed an upward trend. With regard to sentence productivity, MLU showed a trend of increase. In terms of grammatical accuracy, the proportion of well-formed utterances showed a declining trend, but no single word utterances were produced. As for error types and numbers, the participant made more phonological and lexical errors. Results from the short-term microstructure analysis of the MAIN for P4 are shown in Table 6.

*(2) Long-Term Outcomes (i.e., Two Months Posttreatment).* At follow-up, P4 produced an overall lower number of narrative words compared to baseline. This was the case for closed class words and nouns. On the other hand, she produced more prepositions compared to baseline. Sentence productivity was similar to that of baseline. The overall percentage of errors and error types reverted to baseline. Results from the long-term microstructure analysis of the MAIN for P4 are shown in Table 6.

*3.2.4. Participant 6 (P6)*

*(1) Short-Term Outcomes (i.e., One Day Posttreatment).* P6 produced a higher number of narrative words in the posttreatment assessment compared to baseline. This was mainly the case for closed class words and adjectives. Sentence productivity increased significantly mainly in the MLU. Grammatical accuracy remained stable in all aspects except for the proportion of well-formed utterances that showed a declining trend. The proportion and types of errors remained stable. Results from the short-term microstructure analysis of the MAIN for P6 are shown in Table 7.

*(2) Long-Term Outcomes (i.e., Two Months Posttreatment).* At follow-up, P6 retained the increasing trend he exhibited in the short-term with regard to the number of narrative words. This was mainly the case for closed class words, adjectives, and prepositions. Regarding sentence productivity, MLU and embedding indices remained increased compared to baseline, while the elaboration index decreased. Grammatical accuracy and the proportion and types of errors remained stable. Results from the long-term microstructure analysis of the MAIN for P6 are shown in Table 7.

*3.3. Quality of Life Outcomes.* Quality of life was assessed once at baseline (i.e., day 1 of study) and at follow-up (i.e., two months posttreatment) in all participants. However, P1 was further assessed at one- and two-year follow-ups. Results from the SAQOL-39g assessment are rounded to two decimal places and reported in Table 8. The observed score fluctuations in QoL domains for P1, P4, P5, and P6 were insignificant. However, P2 showed a moderate decline in the communication score and moderate-significant decline in the psychosocial score at two months posttreatment. P3 showed a moderate decline in the psychosocial score at two months posttreatment.

## 4. Discussion

This study set out to investigate the effectiveness of two rTMS paradigms (i.e., 1 Hz rTMS and cTBS) as standalone

Table 4: Short-term (one day posttreatment) and long-term (two months posttreatment) effects of cTBS on narration outcomes (i.e., functional communication) for participant 2.

| Category | Participant 2 | | | | |
|---|---|---|---|---|---|
| Lexical selection | Pre-TMS 1 | Pre-TMS 2 | Baseline | Post-TMS | Follow-up |
| Closed class | 10 | 21 | 15.50 | 20 | 10 |
| Nouns | 3 | 3 | 3.00 | 4 | 1 |
| Adjectives | 4 | 7 | 5.50 | 11 | 4 |
| Prepositions | 4 | 7 | 5.50 | 6 | 1 |
| Adverbs | 1 | 4 | 2.50 | 16 | 5 |
| Pronouns | 11 | 8 | 9.50 | 14 | 18 |
| Verbs | 18 | 21 | 19.50 | 31 | 18 |
| Sentence productivity | | | | | |
| MLU | 2.55 | 4.44 | 3.49 | 3.40 | 3.17 |
| Elaboration index | 1.06 | 1.75 | 1.40 | 1.21 | 1.53 |
| Embedding index | 0.00 | 0.31 | 0.16 | 0.10 | 0.17 |
| Discourse productivity | | | | | |
| Narrative words | 51 | 71 | 61.00 | 102 | 57 |
| Grammatical accuracy | | | | | |
| Prop of S with V | 18 | 16 | 17.00 | 29 | 15 |
| Prop of U w/o V | 2 | 0 | 1.00 | 0 | 2 |
| Prop of single word U | 0 | 0 | 0.00 | 1 | 1 |
| Prop of well-formed U | 0.94 | 0.75 | 0.85 | 0.79 | 0.33 |
| AUX complexity index | 1.06 | 1.07 | 1.06 | 1.00 | 1.00 |
| Error types | | | | | |
| Phonological | 1 | 1 | 1.00 | 2 | 2 |
| Morphosyntactic | 2 | 0 | 1.00 | 2 | 1 |
| Semantic | 1 | 0 | 0.50 | 0 | 1 |
| Lexical | 2 | 2 | 2.00 | 3 | 3 |
| Neologisms | 0 | 0 | 0.00 | 0 | 0 |
| Circumlocution | 0 | 1 | 0.50 | 0 | 1 |
| Phonological % | 0.02 | 0.01 | 0.02 | 0.02 | 0.04 |
| Morphosyntactic % | 0.04 | 0.00 | 0.02 | 0.02 | 0.02 |
| Semantic % | 0.02 | 0.00 | 0.01 | 0.00 | 0.02 |
| Lexical % | 0.04 | 0.03 | 0.03 | 0.03 | 0.05 |
| Neologisms %: | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Circumlocution % | 0.00 | 0.01 | 0.01 | 0.00 | 0.02 |
| All errors % | 0.12 | 0.06 | 0.08 | 0.07 | 0.14 |

Key: prop: proportion; s: sentences; V: verbs; U: utterances; w/o: without.

treatments for chronic poststroke aphasia in six individuals. Acute and subacute aphasia were both excluded from this study since only in chronic aphasia is there a remarkable slowing in the rate of spontaneous functional recovery [43].

The rationale behind the decision of using rTMS as a standalone treatment was based on (i) previous evidence suggesting that rTMS alone can lead to long-term language recovery in chronic aphasia poststroke [44–46] and (ii) the inconsistencies in SALT approaches (type and intensity) amongst several TMS aphasia studies [3–8, 20–23].

The decision to use two rTMS paradigms (i.e., cTBS and 1 Hz rTMS) was made in order to explore whether such protocols would induce similar changes in language performance in the sample under investigation, since both neuromodulation paradigms exert the same neurophysiological effects on the human brain (i.e., suppression of neuronal activity) even though they differ in the duration of TMS conditioning.

The trial followed a single study experimental design (SSED) in which all participants underwent two baseline measurements, then received 10 daily sessions of rTMS, and were reassessed one day and two months posttreatment. Participant 1 was further reassessed one- and two years posttreatment. The rest of the participants were not reassessed after the two-month follow-up period for several reasons (P3, P4, and P5 started one-to-one speech therapy; P2 lost interest as he did not observe any functional improvement; P6 started group aphasia therapy). More recently, it was

Table 5: Short-term (one day posttreatment) and long-term (two months posttreatment) effects of cTBS on narration outcomes (i.e., functional communication) for participant 3.

| Category | Participant 3 | | | | |
|---|---|---|---|---|---|
| Lexical selection | Pre-TMS 1 | Pre-TMS 2 | Baseline | Post-TMS | Follow-up |
| Closed class | 21 | 22 | 21.50 | 25 | 33 |
| Nouns | 17 | 19 | 18.00 | 21 | 29 |
| Adjectives | 4 | 2 | 3.00 | 1 | 5 |
| Prepositions | 5 | 5 | 5.00 | 7 | 7 |
| Adverbs | 3 | 2 | 2.50 | 0 | 2 |
| Pronouns | 6 | 8 | 7.00 | 4 | 8 |
| Verbs | 19 | 19 | 19.00 | 19 | 23 |
| Sentence productivity | | | | | |
| MLU | 5.36 | 6.42 | 5.89 | 6.42 | 5.35 |
| Elaboration index | 2.31 | 2.92 | 2.61 | 2.67 | 2.25 |
| Embedding index | 0.36 | 0.58 | 0.47 | 0.58 | 0.15 |
| Discourse productivity | | | | | |
| Narrative words | 75 | 77 | 76.00 | 77 | 107 |
| Grammatical accuracy | | | | | |
| Prop of S with V | 13 | 12 | 12.50 | 12 | 20 |
| Prop of U w/o V | 1 | 0 | 0.50 | 0 | 0 |
| Prop of single word U | 0 | 0 | 0.00 | 0 | 0 |
| Prop of well-formed U | 0.38 | 0.42 | 0.40 | 0.75 | 0.60 |
| AUX complexity index | 1.07 | 1.00 | 1.04 | 1.17 | 1.05 |
| Error types | | | | | |
| Phonological | 26 | 25 | 25.50 | 21 | 28 |
| Morphosyntactic | 3 | 2 | 2.50 | 4 | 5 |
| Semantic | 0 | 1 | 0.50 | 0 | 0 |
| Lexical | 4 | 0 | 2.00 | 0 | 3 |
| Neologisms | 4 | 4 | 4.00 | 0 | 0 |
| Circumlocution | 0 | 0 | 0.00 | 0 | 2 |
| Phonological % | 0.35 | 0.32 | 0.34 | 0.27 | 0.26 |
| Morphosyntactic % | 0.04 | 0.03 | 0.03 | 0.05 | 0.05 |
| Semantic % | 0.00 | 0.01 | 0.01 | 0.00 | 0.00 |
| Lexical % | 0.05 | 0.00 | 0.03 | 0.00 | 0.03 |
| Neologisms % | 0.05 | 0.05 | 0.05 | 0.00 | 0.00 |
| Circumlocution % | 0.00 | 0.00 | 0.00 | 0.00 | 0.02 |
| All errors % | 0.49 | 0.42 | 0.45 | 0.32 | 0.36 |

Key: prop: proportion; s: sentences; V: verbs; U: utterances; w/o: without.

alleged that two pretherapy probes can track the level of performance and rate of change [41]. In the present study, two baseline measurements were applied to lessen concerns that the observed effects may be due to random variation in subject performance and also to minimize placebo effects [42]. Furthermore, participants were blind to their status of TMS conditioning (real vs. sham) until the end of the study. Crucially, none of the six participants experienced any side effects during or after TMS conditioning.

Results from the present study corroborate findings from other studies that have successfully used TBS paradigms [13, 14, 16] revealing that cTBS and 1 Hz rTMS bring about comparable changes in language performance. In the short-term (i.e., one day posttreatment), all participants but one (P5 with global aphasia) showed trends towards improvement in several language skills. In the long-term (i.e., two months posttreatment), three participants showed trends towards improvement in various language skills. All three participants with anomic aphasia exhibited trends of improvement in comprehension (one in the short-term, one in the long-term, and one in the short- and long-term); two showed trends of improvement in reading (one in the short-term and one in the short- and long-term), and two showed trends towards improvement in naming (one in the short-term and one in the long-term). One participant (P1 with global aphasia) showed overall improvements in comprehension and reading at two months and at one-year follow-up [42] that were sustained two years posttreatment as well. Notably, this was the

Table 6: Short-term (one day posttreatment) and long-term (two months posttreatment) effects of 1 Hz rTMS on narration outcomes (i.e., functional communication) for participant 4.

| Category | Participant 4 | | | | |
|---|---|---|---|---|---|
| Lexical selection | Pre-TMS 1 | Pre-TMS 2 | Baseline | Post-TMS | Follow-up |
| Closed class | 15 | 21 | 18.00 | 26 | 7 |
| Nouns: | 11 | 21 | 16.00 | 20 | 6 |
| Adjectives | 0 | 7 | 3.50 | 2 | 0 |
| Prepositions | 0 | 1 | 0.50 | 1 | 6 |
| Adverbs | 1 | 1 | 1.00 | 0 | 0 |
| Pronouns | 14 | 8 | 11.00 | 6 | 13 |
| Verbs | 11 | 17 | 14.00 | 12 | 10 |
| Sentence productivity | | | | | |
| MLU | 3.50 | 4.00 | 3.75 | 4.86 | 3.23 |
| Elaboration index | 2.38 | 1.53 | 1.95 | 1.64 | 1.60 |
| Embedding index | 0.14 | 0.05 | 0.10 | 0.07 | 0 |
| Discourse productivity | | | | | |
| Narrative words | 52 | 76 | 64,00 | 68 | 42 |
| Grammatical accuracy | | | | | |
| Prop of S with V | 8 | 15 | 11.50 | 11 | 10 |
| Prop of U w/o V | 3 | 2 | 2.50 | 3 | 1 |
| Prop of single word U | 3 | 2 | 2.50 | 0 | 2 |
| Prop of well-formed U | 0.50 | 0.27 | 0.38 | 0.09 | 0.50 |
| AUX complexity index | 1.00 | 1.00 | 1.00 | 0.90 | 1.00 |
| Error types | | | | | |
| Phonological | 0 | 2 | 1.00 | 6 | 1 |
| Morphosyntactic | 3 | 14 | 8.50 | 14 | 2 |
| Semantic | 0 | 5 | 2.50 | 4 | 3 |
| Lexical | 0 | 1 | 0.50 | 3 | 2 |
| Neologisms | 1 | 1 | 1.00 | 0 | 1 |
| Circumlocution | 0 | 0 | 0.00 | 1 | 0 |
| Phonological % | 0.00 | 0.03 | 0.02 | 0.09 | 0.02 |
| Morphosyntactic % | 0.06 | 0.18 | 0.13 | 0.21 | 0.05 |
| Semantic % | 0.00 | 0.07 | 0.04 | 0.06 | 0.07 |
| Lexical % | 0.00 | 0.01 | 0.01 | 0.04 | 0.05 |
| Neologisms % | 0.02 | 0.01 | 0.02 | 0.00 | 0.02 |
| Circumlocution % | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 |
| All errors % | 0.08 | 0.30 | 0.21 | 0.41 | 0.21 |

Key: prop: proportion; s: sentences; V: verbs; U: utterances; w/o: without.

oldest participant who exhibited severe global aphasia resulting from diffuse left hemispheric lesions that also had the least years of education (i.e., six) compared to the other participants. No decline in linguistic and cognitive performance compared to baseline was observed in any participant. Also, none of the participants showed any (trend towards) improvement in the control variable (i.e., problem-solving skills). The control variable was assessed at baseline as many times (i.e., two) as the dependent language variables (i.e., comprehension, expression, reading, and naming accuracy) in all participants, and as it remained stable in all participants, it was assumed that (i) the chances that TMS led to language specific gains were increased and (ii) the possibilities for the placebo and training effects were reduced.

To date, three studies have shown that 1 Hz (LF) rTMS as a standalone therapy can lead to language gains in some PWA. In particular, one study [44] investigated the effects of 1 Hz rTMS on naming performance and noticed immediate and long-lasting improvements (6 months posttreatment) in nine individuals with mild-to-moderate chronic nonfluent aphasia. In the present study, along with two participants that had anomic aphasia and exhibited trends towards improvement in naming, the participant with Broca's aphasia also showed a trend of improvement in naming, however only in the short-term. In another study, improvements in several language skills (i.e., naming, repetition, picture description tasks, and length of utterances) were observed that lasted up to 12 months post (1 Hz)-rTMS

Table 7: Short-term (one day posttreatment) and long-term (two months posttreatment) effects of 1 Hz rTMS on narration outcomes (i.e., functional communication) for participant 6.

| Category | | | Participant 6 | | |
|---|---|---|---|---|---|
| Lexical selection | Pre-TMS 1 | Pre-TMS 2 | Baseline | Post-TMS | Follow-up |
| Closed class | 22 | 30 | 26.00 | 41 | 41 |
| Nouns | 17 | 26 | 21.50 | 27 | 24 |
| Adjectives | 3 | 3 | 3.00 | 10 | 12 |
| Prepositions | 6 | 6 | 6.00 | 8 | 13 |
| Adverbs | 3 | 3 | 3.00 | 3 | 2 |
| Pronouns | 4 | 5 | 4.50 | 4 | 3 |
| Verbs | 14 | 21 | 17.50 | 23 | 22 |
| Sentence productivity | | | | | |
| MLU | 6.56 | 6.00 | 6.28 | 9.67 | 8.83 |
| Elaboration index | 3.33 | 2.93 | 3.13 | 4.17 | 1.83 |
| Embedding index | 0.5 | 0.38 | 0.44 | 0.92 | 0.85 |
| Discourse productivity | | | | | |
| Narrative words | 69 | 94 | 81.5 | 116 | 117 |
| Grammatical accuracy | | | | | |
| Prop of S with V | 9 | 15 | 12 | 11 | 12 |
| Prop of U w/o V | 1 | 1 | 1 | 1 | 1 |
| Prop of single word U | 0 | 0 | 0 | 0 | 0 |
| Prop of well-formed U | 0.89 | 0.93 | 0.91 | 0.73 | 0.83 |
| AUX complexity index | 1.11 | 1.07 | 1.09 | 1.00 | 1.00 |
| Error types | | | | | |
| Phonological | 4 | 0 | 2.00 | 0 | 0 |
| Morphosyntactic | 3 | 0 | 1.50 | 1 | 2 |
| Semantic | 0 | 3 | 1.50 | 0 | 4 |
| Lexical | 1 | 2 | 1.50 | 2 | 2 |
| Neologisms | 0 | 0 | 0.00 | 0 | 0 |
| Circumlocution | 0 | 0 | 0.00 | 1 | 0 |
| Phonological % | 0.06 | 0.00 | 0.02 | 0.00 | 0.00 |
| Morphosyntactic % | 0.04 | 0.00 | 0.02 | 0.01 | 0.02 |
| Semantic % | 0.00 | 0.03 | 0.02 | 0.00 | 0.03 |
| Lexical % | 0.01 | 0.02 | 0.02 | 0.02 | 0.02 |
| Neologisms % | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Circumlocution % | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 |
| All errors % | 0.12 | 0.05 | 0.08 | 0.03 | 0.07 |

Key: prop: proportion; s: sentences; V: verbs; U: utterances; w/o: without.

in six people with chronic nonfluent aphasia poststroke [45]. In the present study, one participant with severe global aphasia showed sustained improvements in comprehension and reading two months, one year, and two years posttreatment. In another trial [46], an increase in the number of closed-class words of discourse productivity was noticed in 10 individuals with chronic nonfluent aphasia two months posttreatment with 1 Hz rTMS. In our study, the analysis of narratives yielded mixed results. With regard to error types and percentages, the participant with Broca's aphasia (P3) exhibited less phonological errors and neologisms in the short-term and less neologisms in the long-term. On the other hand, one of the participants with moderate-severe anomic aphasia (P4) made more phonological and lexical errors in the short-term but reverted to baseline performance in the long-term. Discourse productivity increased in the short-term in one participant with moderate-severe anomic aphasia (P2) and in the long-term in the participant with Broca's aphasia (P3). The participant with mild anomic aphasia (P6) showed improvement in the short-term that was also sustained in the long-term. Finally, one of the participants with moderate-severe anomic aphasia (P4) showed a declining trend only in the long-term. Interestingly, the participant with mild anomic aphasia (P6) manifested an increase in his MLU both in the short- and long-term.

Up until now, several TMS randomized controlled trials (RCTs) have indicated that 1 Hz rTMS over the contralesional IFG in conjunction with SALT has the potential to

Table 8: Quality of life at the pretreatment (baseline) stage and at 2 months follow-up using the SAQOL-39g for all participants and at baseline, at 2 months follow-up, at 1 year follow-up, and at 2 years follow-up for participant 1.

| Item (maximum score: 5) | Participant 1 | | | | Participant 2 | | Participant 3 | | Participant 4 | | Participant 5 | | Participant 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 2 months post-TMS | 1 year post-TMS | 2 years post-TMS | Baseline | 2 months post-TMS | Baseline | 2 months post TMS | Baseline | 2 months post TMS | Baseline | 2 months post TMS | Baseline | 2 months post TMS |
| SAQOL-39g mean score | 2.05 | 2.18 | 2.12 | 1.9 | 3.57 | 3.1 | 4.03 | 3.82 | 3.32 | 3.2 | 1 | 1 | 4.24 | 4.28 |
| Physical score | 2.38 | 2.44 | 2.25 | 2.1 | 4.62 | 4.43 | 5 | 5 | 4.68 | 4.5 | 1 | 1 | 4.75 | 4.81 |
| Communication score | 1.57 | 1.72 | 1.85 | 1.6 | 2.71 | 2.28 | 3.28 | 3.14 | 2.42 | 2.1 | 1 | 1 | 4.71 | 4.71 |
| Psychosocial score | 2.2 | 2.38 | 2.25 | 2 | 3.37 | 2.56 | 3.81 | 3.31 | 2.87 | 3 | 1 | 1 | 3.25 | 3.31 |

drive change in various language domains in at least some people with subacute [3–5, 8, 22, 23] and chronic aphasia [11, 21]. Nonetheless, there are several inconsistencies in those studies concerning the site of stimulation within the homologue of Broca's area; the methods of localization of the stimulation site; the ingredients, dosage, and intensity of the adjunct SALT; the number and types of language outcomes measures; and the number and duration of follow-up assessments. In addition, not all studies have reported positive outcomes. For example, a most recent RCT [47] did not find any beneficial add on effects of 1 Hz rTMS to SALT in chronic poststroke aphasia rehabilitation. Another study raises concerns about applying LF TMS over the right pTr in patients with apraxia of speech (AoS) [48]. In this study, the researchers demonstrated that a 69-year-old individual with AoS due to a left first ever small ischemic stroke of the left precentral gyrus deteriorated after one session of real cTBS over the contralesional precentral gyrus and improved after sham cTBS over the same area according to both objective and subjective evaluations. The findings of those trials highlight the possible impact of lesion location on noninvasive neuromodulation response and point towards the development of individualized rTMS aphasia rehabilitation protocols by considering individual-intrinsic variables (age at the time of stroke, lesion volume and location, white matter integrity, and cognitive-linguistic impairment) and individual extrinsic variables (e.g., environment, treatment mode, language, and brain recovery) [49], rather than providing a "one-size fits all" neuromodulation approach. Furthermore, such findings imply that expressive language processes rely on cortical networks that involve both hemispheres.

In addition to RCTs supporting the potential benefit of LF rTMS on aphasia rehabilitation poststroke, some systematic reviews with/without meta-analyses are also supportive [50–53]. However, other recent work has indicated that the quality of the conduct of reviews 50-53 is low, and therefore, more research is needed [54]. More recently, a meta-analysis of RCTs and randomized cross-over trials [55] found a moderate long-term effect size of rTMS effects in language gains especially in naming in both subacute and chronic patients with aphasia. In this review, five studies applied LF rTMS, one study combined LF with HF rTMS, and one study compared LF with HF and sham TMS (see [55] and references within).

Overall, research in the field of 1 Hz rTMS to the contralesional IFG in aphasia recovery is ongoing but is also parallel to trials investigating the effects of different paradigms, either in terms of stimulation sites and/or TMS paradigms per se. For example, an emerging number of studies have started exploring inhibitory cTBS over the contralesional IFG [15, 25, 56], excitatory iTBS over perilesional areas of the left hemisphere [12, 13, 16], and sequential cTBS and iTBS [14].

Aphasia-related TMS research is flourishing, and TMS technology has now become a mainstream application in many aphasia labs worldwide. The challenge researchers are facing is the unravelment of the mechanisms of TMS-induced language recovery and the understanding of why some people respond (more or less) whilst others do not respond to this neuromodulation technique. Despite numerous clinical studies that have explored the therapeutic potential of rTMS in several neurological disorders, the cellular and molecular mechanisms responsible for the after-effects of rTMS are largely unknown. The mixture of LTD and LTP effects on synapses measured by MEP behavioral changes is highly variable across individuals, showing that it would be an oversimplification to describe the rTMS after-effects as LTD or LTP-like plasticity solely based on MEP modifications [57]. Additional research is needed to elucidate how structural and functional properties of individual neurons and local networks are related to the effects of single pulse rTMS [58]. Beyond the molecular mechanisms underlying behavioral recovery, a few insightful accounts about the underpinnings of the observed TMS-induced language improvement, that also explain the rationale behind the application of various aphasia TMS protocols, have been suggested and are based in principle on models of brain reorganization after a stroke.

The first account is related to stroke-induced disruption of the interhemispheric balance. This disruption leads to reduced inhibition from the affected to the unaffected hemisphere and to increased and deleterious inhibition of the affected from the unaffected hemisphere [59]. This process is considered maladaptive for language recovery as it blocks the dominant hemisphere, where language processes are established, from resuming their role in language processes [60]. The decision of applying LF rTMS over the contralesional hemisphere in this research was motivated by the hypothesis that by inhibiting the right hemisphere, residual language supported by the left hemisphere is released from transcallosal inhibitory input by the intact right hemisphere [61].

A second possible scenario is that language gains are associated with recruitment of regions of the right hemisphere that are homotopic to the damaged components of the left language network [62]. A third account is based on the increasingly accepted theory that language processes rely on highly localized brain regions and bilaterally distributed brain networks [63], and language reorganization poststroke is based on domain-specific and domain-general network processes [64]. The hypothesis that the suppression of a hyperactive right pTr with LF rTMS modulates the right pars opercularis (pOp), and in turn, other right brain regions may explain the results of the present study.

In addition to the unravelment of the neural mechanisms of TMS-induced language recovery, cognitive and psycholinguistic analyses demonstrating which cognitive processes are implicated in language facilitation and where in the language system, rTMS induces language improvements, may provide researchers with an insight into the issue of candidacy for and responsiveness to TMS. On this basis, research is poor as most clinical aphasia studies focus on the mechanistic aspects of recovery (i.e., neuroanatomical and behavioral changes). Some explanations however provide evidence on how the language system is reorganized post-TMS. It is postulated that the observed improvement in discourse productivity in chronic nonfluent aphasia may be explained by TMS-induced improved lexical-semantic access allowing retrieval of word- and word meaning

representations [46]. This could explain the noticeable improvement in accessing words in several categories and no improvement in grammatical complexity or sentence construction [46]. In the present study, there was only one participant with nonfluent aphasia who showed improvement in discourse productivity in the long-term and the above account may explain his performance.

The current study has several strengths as follows. First, we suggest adopting an SSED methodology in aphasia research and using WEST statistics to measure treatment change as such statistics are suitable for studies with small numbers of participants and nonhomogenous profiles. Second, we performed follow-up assessments to investigate the long-term effects of TMS treatment. In fact, one participant was followed up for two years posttreatment and demonstrated sustained language gains in comprehension and reading skills in that period. The findings corroborate prior evidence that TMS can lead to sustained language changes without any additional behavioral therapy [44–46]. Third, this study employed an ecologically valid measure to assess functional communication which is related to phrase and sentence production and narration and not experimental language tasks. Finally, as stroke affects health-related QoL [65], the effects of treatment on the QoL of the participants were also assessed. Proxy ratings were used as three participants struggled to respond to questions due language comprehension problems. Existing evidence supports that proxies exaggerate QoL problems of patients [66]. Hence, caution is needed when proxies contribute to QoL assessments. Nonetheless, when patient reports cannot be obtained, proxies can be helpful [67]. In the current study, the findings indicated that QoL did not significantly change in three participants because of the treatment. For the remaining participants, posttreatment communication scores showed a declining trend in three participants and the psychological scores dropped for two others. Such findings clearly capture the difference between statistical and clinical significance. Statistical significance is important for researchers and service providers but is of little value to patients and their families. Clinical significance is vital for the person with communication problems and their caregivers. Based on the results from the QoL measure, treatment results failed to meet the needs and expectations of the participants and their families. Therefore, we strongly recommend that future TMS aphasia studies are also aimed at capturing the clinical significance of this type of treatment using relevant tools.

Despite the promising results of this study, there are several limitations that warrant discussion. First, the sample size was small, and the participants had various clinical profiles. This compromises the generalizability of our findings, but on the other hand, this clinical profile heterogeneity can be seen as advantageous as it is typical of what is observed in clinical settings. Also, the fact that the TMS protocol was the same for all participants (i.e., inhibitory rTMS) allowed insight into who may benefit more from this particular protocol. It seems, for example, that it could prove beneficial for global aphasia on the grounds of diffuse left hemisphere damage. However, as direct measurements of brain activation and connectivity were not obtained, no hypotheses could be formulated regarding which model(s) of brain-reorganization best explain(s) the findings. In TMS aphasia research, direct measures of brain activation and connectivity are needed to help with the elucidation of the neuroplastic effects of treatments [42]. Realistically though, individual fMRI localization is expensive, time consuming, and not available in all aphasia labs.

We suggest that to enhance the effectiveness of rTMS in aphasia rehabilitation, future studies should systematically document all their data in an Aphasia TMS Database similar to the PLORAS (predicting language outcome and recovery after stroke) project [68]. In particular, with regard to participants' intrinsic factors, parameters such as age, lesion location and size, vascular perfusion, brain connectivity and integrity of white matter, genetics, body mass indices, sex, handedness, education, type of aphasia, and its severity should all be documented as there is robust evidence that they all affect aphasia recovery. For instance, with regard to age, there is evidence that young people with aphasia improve more compared to older individuals [69]. Regarding lesion location, some studies suggest that lesions involving the left STG (superior temporal gyrus) and Wernicke's area are associated with poor aphasia improvement [70]. With regard to lesion magnitude, even though large left hemisphere lesions are typically associated with poorer recovery [71], in a recent study, patients with larger stroke volumes showed greater aphasia improvements regardless of the involvement of the language areas [72]. This could explain the findings from the current study in which the only participant who showed statistically significant improvements had diffuse and large brain lesions in the left hemisphere. In addition, several studies have shown shifts in vascular perfusions poststroke [73, 74], but the extent to which such alterations influence recovery of the neural networks for language is unknown [49]. Furthermore, the degree of white matter integrity in the infarcted hemisphere together with the integrity of white matter tracts in the contralesional hemisphere is also likely to be linked to recovery ([49] and references within). Research on the role of BDNF (brain-derived neurotrophic factor) variants on language recovery poststroke is emerging, and several studies have demonstrated that it influences recovery [75, 76]. Also, through univariate analysis, it has been shown that total lean body mass—not adipose tissue—may be a positive factor for predicting aphasia improvement [72]. Lastly, evidence in relation to the impact of sex [77], handedness, and educational background [78] on language recovery is controversial.

Aphasia severity has been shown to be a good predictor of recovery of both short- [79] and long-term outcomes [80]. It is postulated that all the above biological (intrinsic) factors have a synergistic effect on language recovery poststroke, and this can be verified by the observed variability in progression of aphasia and recovery even between people with the same type of aphasia. In addition, TMS parameters (e.g., type of coil, stimulation site, duration, dosage, intensity, and frequency of the stimulation) also affect outcomes. In particular, the amount of surface charge produced and thus the extent of action of the current in the brain tissue

depend on many biological and physical parameters such as the magnetic pulse waveform, the intensity, frequency and pattern of stimulation, the type and orientation of coil, the distance between coil and brain, and the respective orientation of the current lines and excitable neuronal elements into the brain [43]. For example, if the handle of f8c is oriented parallel to the interhemispheric midline (posteroanterior direction), motor cortex TMS activates the pyramidal tract only indirectly through interneurons [81]. When the handle of an f8c is oriented perpendicular to the interhemispheric midline (lateromedial direction), both interneurons and pyramidal neurons are activated [82]. The lowest intensity threshold to elicit MEPs in the M1 is achieved when the stimulus creates a posteroanterior current that is orthogonal to the central sulcus (i.e., the handle of the f8c oriented 45° posteriorly and laterally) [83], but the reverse orientation (anteroposterior) makes the latency time increase by several milliseconds [43] and is considered better for inducing motor cortex plasticity [84]. To optimize the effects of TMS, it is suggested that the strength of the electric field perpendicular to the targeted area (for all cortical surface areas) is maximised [85]. Also, even though MEP measurements in healthy individuals have led to the consensus that low-frequency stimulation (≤1 Hz) induces inhibition, whereas high frequencies (≥ 5 Hz) induce excitation [43], both conditions may lead to mixed effects [86]. By doubling, for example, the duration of stimulation on the motor cortex inhibition may reverse to excitation and vice versa [87]. Moreover, SALT is the gold standard in aphasia rehabilitation [88], and the above discussion demonstrates the high variability and lack of standardization of SALT approaches in the field of aphasia rehabilitation [89]. The effectiveness of SALT approaches first needs to be evaluated against standards of evidence-based practice (EBP). Until then, researchers are prompted to use structured aphasia programs as adjuncts to TMS based on the evidence that this leads to neuroplastic changes that support aphasia recovery.

## 5. Conclusion

The advent of modern noninvasive brain stimulation techniques has shifted the attention of aphasia rehabilitation scientists to additional ways that could enhance plasticity in the lesioned language brain network. Even though the number of studies that have applied TMS in poststroke aphasia rehabilitation is increasing, results remain controversial. From the current findings, it can be concluded that inhibitory TMS over the right pTr has the potential to drive neuroplastic changes that facilitate language recovery in chronic poststroke aphasia. However, to elucidate the precise mechanisms of action that TMS exerts in the lesioned language network, researchers are urged to experiment with different protocols and follow up their participants for potential long-term and generalization effects. The importance of the clinical relevance of therapies urges future researchers to include ecological outcome measures that capture the effects of TMS aphasia treatment on everyday communication.

## Data Availability

The data of the present study are available from the corresponding author upon rational request.

## Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

## Acknowledgments

This work was cofunded by the European Regional Development Fund and the Republic of Cyprus through the Research and Innovation Foundation (Project: EXCELLENCE/1216/0517). We thank Mr. Karayiannis Demetris, clinical linguist (M.Sc., B.A.), for his contribution to the analysis of linguistic data.

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Hindawi
Behavioural Neurology
Volume 2021, Article ID 3419907, 12 pages
https://doi.org/10.1155/2021/3419907

*Review Article*

# Therapeutic Application of rTMS in Atypical Parkinsonian Disorders

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Received 30 April 2021; Accepted 3 December 2021; Published 23 December 2021

Academic Editor: Muh-Shi Lin



The terms atypical parkinsonian disorders (APDs) and Parkinson plus syndromes are mainly used to describe the four major entities of sporadic neuronal multisystem degeneration: progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), and dementia with Lewy bodies (LBD). APDs are characterized by a variety of symptoms and a lack of disease modifying therapies; their treatment thus remains mainly symptomatic. Brain stimulation via repetitive transcranial magnetic stimulation (rTMS) is a safe and noninvasive intervention using a magnetic coil, and it is considered an alternative therapy in various neuropsychiatric pathologies. In this paper, we review the available studies that investigate the efficacy of rTMS in the treatment of these APDs and Parkinson plus syndromes. The majority of the studies have shown beneficial effects on motor and nonmotor symptoms, but research is still at a preliminary phase, with large, double-blind studies lacking in the literature.

## 1. Introduction

*1.1. Atypical Parkinsonian Disorders/Parkinson plus Syndromes.* Progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), and Lewy body dementia (LBD) are the most important entities of the neurodegenerative disorders consisting the atypical parkinsonian disorders (APDs) or the so-called "Parkinson Plus" syndromes. The clinical phenotypes of these syndromes present great heterogeneity, as a result of the different underlying pathophysiological mechanisms. These disorders manifest as an atypical parkinsonian syndrome with symmetric distribution, rapid deterioration, and poor response to medications (levodopa or other dopaminergic agonists). In addition to parkinsonism, other atypical clinical symptoms are also present, such as supranuclear gaze palsy, asymmetrical apraxia, early postural instability, early dementia, and symptoms from the autonomic system [1, 2]. APD sare subdivided into "synucleinopathies" and "tauopathies," based on the abnormally accumulated protein that contributes to the neurodegenerative damage (i.e., a-synuclein or Tau). MSA and LBD are considered synucleinopathies, while PSP and CBD are tauopathies. Although APDs are rarer disorders than PD, the differential diagnosis is very important, since disease deterioration and functional deficits usually appear earlier than in PD [3], and classic PD therapies are only partially beneficial.

The most common of the atypical parkinsonian syndromes is PSP and is usually difficult to distinguish from PD. Early postural instability and falls, accompanied by an

akinetic rigid syndrome and ocular dysfunction, are the most common and typical expressions of this disorder [2, 4, 5]. These symptoms characterized the phenotype of PSP now called Richardson's syndrome (PSP-RS). Until the 2017 update, the criteria for the clinical differential diagnosis of PSP had remained unchanged since 1990 [4]. The 2017 update emphasized that PSP encompasses a number of different clinical phenotypes and outlined ten, with Richardson's syndrome (PSP-RS) being only one among those ten [6]. Pathophysiologically, PSP features an overexpression of a particular tau protein isoform, the 4R-tau, which contains four microtubule-binding repeat domains [7–9]. The tufted astrocyte is the most common pathological abnormality in PSP, while neurofibrillary tangles (NFTs) and coiled bodies usually contribute to the pathology as well [10]. The different localization of tau protein accumulation drives the different clinical phenotypes. Brainstem pathology is expressed with pure akinesia, while cortical pathology creates a focal cortical syndrome [7]. Studies have revealed an important involvement of cerebellar structures in PSP pathology, and especially the dentate nucleus, despite cerebellar signs in this disorder being rare [4].

MSA is a neurodegenerative disorder, manifesting with parkinsonism, cerebellar ataxia, and autonomic dysfunction [11]. Based on the predominant symptoms, two main MSA phenotypes are distinguished: the MSA-C with predominant cerebellar symptoms and the MSA-P with predominant parkinsonian manifestations [11, 12]. Sleep changes (particularly R*EM* sleep behavior disorders), autonomic failure, and respiratory dysfunction are common in both subtypes and can precede motor symptoms even for years [13]. MSA, as already mentioned, belongs to the synucleinopathies, and its pathology is characterized by glial cytoplasmatic inclusions formed by fibrillated $\alpha$-synuclein proteins in the striato-nigral and olivo-ponto-cerebellar areas [14].

CBD is a rare degenerative neurological disorder pathologically characterized by asymmetrical cortical brain atrophy, usually more pronounced at the frontoparietal regions, combined with degenerated basal ganglia. The term CBD describes the pathology of a disease which usually but not always coexists with clinical symptoms encompassed by the corticobasal syndrome (CBS). The CBS phenotype usually includes asymmetric hand dysfunction, bradykinesia, dysphagia, tremor, rigidity, dystonia, and gait and postural instability in the spectrum of motor symptoms, while cognitive impairment, visuospatial deficits, and apraxia constitute the nonmotor spectrum [15].

Finally, LBD comes after Alzheimer's disease (AD), as the second most frequent neurodegenerative dementia, encompassing dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) [16]. The pathological characteristic of this disorder is the aggregation of a-synuclein, creating the so-called Lewy bodies. Parkinsonism, cognitive impairment, serious behavioral disorders, vivid and recurrent hallucinations, and sensitivity to antipsychotic medications are the most common and typical symptoms [17].

Another common element of these entities is the absence of disease-modifying drugs (DMDs) or other treatment options that are effective in this regard [16]. The treatment of APDs remains largely symptomatic, for example, with botulinum injections when dystonia manifests [18], while levodopa is either ineffective or effective for a short period of time [19], so no amelioration in parkinsonism symptoms can be easily achieved. It is thus evident that safe and effective treatment options are urgently needed. A new research field that has been gaining more ground in this direction is the application of transcranial magnetic stimulation (TMS).

*1.2. TMS Principles.* In 1985, TMS was firstly introduced in the group of noninvasive brain stimulation techniques [20]. TMS uses a magnetic coil targeting the scalp and producing a high-intensity pulse, which stimulates neurons. Depending on the exact protocol and the different coil parameters, the stimulation of the neurons can vary, giving way to many different intervention potentials [21].

In pathophysiological studies, single and paired stimuli are usually applied, contrary to studies investigating the therapeutic use of TMS, which apply a series of repetitive stimuli [repetitive TMS (rTMS)]. rTMS applied at set frequencies or patterns can alter cortical excitability, lasting long after the end of the stimulation [22]. rTMS can induce long-lasting changes through its effect on blood circulation within the CNS, neuronal metabolism, and excitability of the cortex directly receiving the stimulation and of areas connected to the target of the stimuli [22–24]. In general, the stimulation of the brain modulates the plasticity of the cortex. These changes are induced via long-term potentiation (LTP) and long-term depression (LTD) [22]. Frequency, duration, and intensity are some of the basic parameters which characterize a stimulation protocol, and its effects can be either excitatory or inhibitory. *H*igh frequency rTMS (HF-rTMS) (>1 Hz) induces LTP and increases cortical excitability, while the application of low-frequency stimulation (LF-rTMS) ($\leq$1 Hz) produces LTD and a decline in cortical excitability [25].

Additionally, rTMS protocols can be further subdivided into simple protocols with identical interstimulus intervals (ISI) between the pulses and patterned protocols with different ISIs. Theta burst stimulation (TBS) belongs to the patterned group. TBS modulates cerebral cortical function, via HF-rTMS that mimics the theta brain waves, consisting of three 50 Hz pulses every 200 ms. TBS application includes two different protocols, the intermittent TBS (iTBS) and the continuous TBS (cTBS); the former increases cortical excitability while the latter decreases it [26].

The use of TMS has been associated with some adverse effects. Transient headaches and scalp discomfort are the most common, and are linked to the activation of scalp pericranial muscles [27]. Furthermore, changes in mood (cases of inducted mania), burns of the scalp, and seizures are the most severe side effects [27, 28]. However, these adverse events are extremely rare, so rTMS is generally considered a safe treatment modality.

rTMS has been considered to be a therapeutic option for many pathologies, such as depression, migraine, and epilepsy [29–31], and even neurodegenerative conditions with cognitive sequelae, such as Alzheimer's disease [32]. In

Table 1: Studies assessing the effects of rTMS in PSP.

| Author, year | Type of study | Study design | Results |
|---|---|---|---|
| Brusa et al. [34] | Prospective cohort study/ open label | (i) 10 PSP patients, 10 PD patients, 10 HC<br>(ii) Lateral cerebellum bilaterally<br>(iii) ITBS protocol (3 50 Hz pulses, repeated at a rate of 5 Hz, 20 trains of 10 bursts in 8 s intervals, 600 pulses, 80% of AMT intensity) for two weeks<br>(iv) Assessment at baseline and after 2 weeks via rs-fMRI and PSP-RSc | (i) Clinical improvement (dysarthria, gait) and a parallel enhancement in functional connectivity between the cerebellar hemisphere and motor cortex<br>(ii) No adverse events |
| Dale et al. [35] | 2 PSP study cases/sham controlled | (i) 2 PSP patients<br>(ii) Cerebellum<br>(iii) RTMS (10 Hz, 4.000 pulses, 4 seconds on, 8 seconds off, 100 trains, 90-110% of RMT intensity) 10 days active 10 days sham stimulation, separated by a month<br>(iv) Assessment at baseline and immediately after treatment | (i) CBI increased/improvement in stability and speech<br>(ii) Pending tolerability |
| Pilotto et al. [36] | Double blind/ sham controlled | (i) 20 PSP patients<br>(ii) Cerebellum<br>(iii) TBS (3 50 Hz pulses repeated at a rate of 5 Hz, 20 trains of 10 bursts in 8 s intervals, 600 pulses, 80% RMT intensity)<br>(iv) Clinical evaluation (Tinetti test, the Short Physical Performance Battery (SPPB), the Timed Up and Go test, and the Functional Reach test (FR)) and static balance assessed before and after active and sham stimulation, inertial sensor unit (IMU) processing accelerator signals | (i) Beneficial effect on postural instability and improvement in area, velocity, acceleration, and jerkiness of sway<br>(ii) No adverse events |
| Santens et al. [37] | Prospective cohort study/ open label | (i) 6 PSP patients<br>(ii) Lower limb motor area<br>(iii) RTMS (10 Hz, 1.000 pulses, 5 seconds on, 55 seconds off, 20 trains, 80% of MT intensity) for 5 consecutive days<br>(iv) Assessment with PSP-RSc at baseline and after 5 days | (i) Improvement on the gait and midline symptoms<br>(ii) No adverse events/discomfort during the stimulation |
| Nishida et al. [38] | Prospective cohort study/ open label | (i) 7 PSP patients<br>(ii) Supplementary motor area (SMA)<br>(iii) RTMS (5 Hz, 500 pulses,10 trains, 10 seconds on, 110% of RMT intensity) for 10 days<br>(iv) Assessment using PSP-RSc at baseline and immediately after treatment | (i) Improvement of the PSP-RS by 7 points<br>(ii) No adverse events |
| Major et al. [39] | 1 PSP case study/open label | (i) 1 PSP patient<br>(ii) Bilateral motor cortex area<br>(iii) LF-rTMS (1 Hz, 80% of RMT intensity) 20 min per day, for five consecutive days<br>(iv) Assessment using mechanometry and goniometry at baseline and after 5 days | (i) Increase in the range of motions and in the muscle forces<br>(ii) No adverse events |
| Boulogne et al. [40] | 1 PSP case study/open label | (i) 1 PSP patient<br>(ii) Right dorsolateral prefrontal cortex (DLPFC)<br>(iii) LF-rTMS (1 Hz, 6 trains, 1 min on–30 sec off, 120% of RMT intensity)<br>(iv) Assessment at baseline and immediately after treatment via the Montgomery Asberg Depression Rating scale (MADRS), the State-Trait Anxiety Inventory (STAI), the Lille Apathy Rating Scale (LARS), and the Global Assessment of Functioning (GAF) Scale. The PSP-RSc and the MoCA were assessed before and after the rTMS treatment | (i) Relieve depression/MADS and STAI scores decreased; the LARS and GAF scale scores increased after rTMS<br>(ii) No adverse events |

Table 1: Continued.

| Author, year | Type of study | Study design | Results |
|---|---|---|---|
| Madden et al. [41] | 1 PSP study cases/sham controlled | (i) 1 PSP patient<br>(ii) Left dorsolateral prefrontal cortex (DLPFC)<br>(iii) TDCS<br>(iv) Assessment at baseline and immediately after treatment via language tasks | (i) Improve phonemic fluency and action naming<br>(ii) No adverse events |

Table 2: Studies assessing rTMS in MSA.

| Author, year | Type of study | Study design | Results |
|---|---|---|---|
| Liu et al. [46] | Prospective cohort study/open label | (i) 9 MSA patients<br>(ii) M1 bilaterally lateral cerebellum bilaterally<br>(iii) HF-rTMS (5 Hz, 2000 pulses, 500 for each target, 50 trains, 100% of RMT intensity) for 5 days<br>(iv) Assessment at baseline and after 5 days via fMRI and UMSARS | (i) Improved motor control and increased resting-state complexity within the motor cortex<br>(ii) No adverse events |
| Yildiz et al. [47] | Prospective cohort study/open label | (i) 12 MSA-C patients, 5 AD patients, and 9 healthy controls<br>(ii) Lateral cerebellum<br>(iii) LF-rTMS (1 Hz, 600 pulses, 90% of RMT intensity)<br>(iv) Evaluation in 2 different sessions in the same day using a computerized reaction time (RT) task and SAI responses | (i) Improvement in SAI deficits, improvement in post-rTMS RT values in the MSA-C group in contrast with the pre-rTMS RT<br>(ii) No adverse events |
| Chou et al. [48] | Randomized/ double-blind/sham controlled study | (i) 21 MSA patients<br>(ii) Left M1<br>(iii) HF-rTMS (5 Hz, 1000 pulses, 10 trains, 110% RTM intensity) for 10 days, one session per day<br>(iv) Assessment at baseline and after 5 and 10 days via fMRI and UMSARS-II | (i) Improvement of motor symptoms, increased brain functional connections in the active rTMS group<br>(ii) No adverse events |
| Wang et al. [49] | Prospective cohort/sham controlled study | (i) 15 MSA patients and 18 healthy controls<br>(ii) Left M1<br>(iii) HF-rTMS (5 Hz, 1000 pulses, 10 trains, 110% RTM intensity) over the left M1 over 2 weeks<br>(iv) Assessment at baseline and after 5 and 10 days via fMRI and UMSARS-II | (i) Improvement of motor symptoms, increased activation in the bilateral cerebellum in the active rTMS MSA group<br>(ii) No adverse events |

addition, rTMS has been extensively studied in PD, showing positive effects in motor and nonmotor symptoms and in therapy complications [33]. This review aims to summarize the available literature concerning the therapeutic intervention of rTMS in APDs and to discuss its future applications. Based on our knowledge, it is the first review to investigate the application of rTMS in the entirety of the APDs. Tables 1 and 2 summarize all the available clinical trials studying the therapeutic application of rTMS in PSP and MSA patients, respectively, while studies involving rTMS in CBD and DBL can be found in Table 3.

## 2. Supranuclear Palsy (PSP)

*2.1. Cerebellar Stimulation.* An increasing amount of evidence has supported the involvement of the cerebellum in PSP pathophysiology. Tau isoforms have been shown to accumulate in the cerebellum and lead to reduce cerebellar volumes [7]. In addition, TMS studies have detected an impairment of functional connectivity to the pathway of the contralateral primary motor cortex (M1) and the cerebellar hemispheres [cerebellar brain inhibition (CBI)] [42]. Levodopa can only partially and temporarily alleviate some of the PSP symptoms, such as akinesia and rigidity [43], with postural instability remaining an important problem. Based on these considerations, a line of studies has explored the effectiveness of cerebellar rTMS in PSP.

The first published open-label trial using TBS over the cerebellum of PSP patients was conducted by Brusa et al. [34]. Ten PSP-RS patients entered the study and were then clinically evaluated based on the PSP Rating Scale (PSP-RSc). Two control groups, one of PD patients and another of healthy age-matched subjects, were also enrolled. The cerebellar iTBS protocol (3 50 Hz pulses, repeated at a rate of 5 Hz, 20 trains of 10 bursts in 8 s intervals, 600 pulses, 80% of AMT intensity) was applied bilaterally to the cerebellum

Table 3: Studies assessing rTMS in CBD and LBD.

| Author, year | Type of study | Study design | Results |
|---|---|---|---|
| Shehata et al. [56] | Prospective cohort study/ open label | (i) 26 CBS patients<br>(ii) Motor cortex contralateral to the more affected side<br>(iii) LF-rTMS (1 Hz, 90% of MT intensity), a session 3 times a week for 1 month, every 3 months<br>(iv) Assessment at baseline and every 3 months over 18 months via UPDRS, Addenbrooke's cognitive examination (ACE-R), Unified Dystonia rating scale (UDRS), HRQoL, caregiver burden questionnaire and videotaping | (i) The UPDRS, caregiver burden, and quality of life were improved after 3 months<br>(ii) No adverse events |
| Takahashi et al. [58] | Prospective cohort study/ open label | (i) 167 patients with mood disorder, 6 DLB patients received rTMS<br>(ii) DLPFC bilaterally<br>(iii) LF-rTMS (1 Hz, 110% of MT intensity) over the right DLPFC and HF-rTMS (10 Hz, 100% MT intensity) for the left DLPFC daily for ten days<br>(i) Assessment at baseline and after 10 days via the HAM-D | (i) Improvement of depressive symptoms<br>(ii) No adverse events |

of all subjects for 10 days. Before and after the iTBS application, functional connectivity between the cerebellum and the contralateral M1 (CBI), intracortical facilitation (ICF), short intracortical inhibition (SICI), and short latency afferent inhibition (SLAI) in the contralateral M1 were measured. Resting state functional magnetic resonance (rs-fMRI) was performed, and the PSP-RSc was administered. After the iTBS treatment, all PSP patients significantly improved in dysarthria, and 2 out of 10 patients reported a significant amelioration in gait. Only CBI metrics improved upon stimulation. This study concluded that PSP patients after cerebellar iTBS showed some clinical improvement and a parallel enhancement in functional connectivity between the hemisphere of the cerebellum, the caudate nucleus, and the brain cortex. However, a placebo effect could not be excluded due to the open-label trial design.

The efficacy of rTMS over the cerebellum in PSP was also investigated in a sham-controlled case study by Dale et al. [35]. They performed CBI assessments with neuronavigation before and after cerebellar HF-rTMS or sham TMS in two patients with PSP, collecting posturography data and speech samples before and after the intervention. Quality of speech was assessed via reading a standard passage, and pace of speech, articulatory difficulty, and article and phonemic errors were noted. The exact rTMS protocol included 4,000 pulses delivered over the cerebellum (10 Hz, 90-110% of Resting Motor Threshold (RMT) intensity), with 10 days of active treatment and 10 days of sham, separated by a month. After treatment, CBI increased by 50% in subject 1 and by 32% in subject 2, while stability and speech also presented an improvement. However, a different form of sham stimulation was applied in the two subjects. Patient 2 received sham stimulation from a coil with a magnetic-blocking spacer, whereas patient 1 had the same spacer with extra superficial electrical stimulation. This superficial stimulation could not produce the same burning sensation in the posterior head and neck area as the active one, so patient 1 was able to guess that this was indeed a sham condition. This unexpected placebo effect in patient 1 means that these results must be taken into consideration with even greater caution.

Pilotto et al. [36] conducted a trial which overcame the placebo effect problem. They designed a double-blind study controlled with sham stimulation and assessed postural stability via mobile health technology. Twenty probable PSP patients were included. All subjects received both real and sham TMS intervention in two different sessions, with an interval of two weeks. The exact protocol included repetitive cerebellar TBS (3 50 Hz pulses repeated at a rate of 5 Hz, 20 trains of 10 bursts in 8 s intervals, 600 pulses, 80% of RMT intensity). The sham stimulation was applied with a coil attached by a spacer so that all the circumstances were identical to the real one, and the subjects could not differentiate the two conditions. Clinical evaluation was conducted on all patients before and after each stimulation, with the Tinetti test, the Timed Up and Go test, the Short Physical Performance Battery (SPPB), and the Functional Reach test (FR). Furthermore, four different tasks, with a duration of 30s each, contributed to the assessment of static balance, also conducted before and after each stimulation. These tasks included tandem and semitandem stance with eyes open and closed, and additionally, an inertial sensor unit (IMU) located over the third lumbar segment of spine, processing and calculating acceleration signals, was also used. Active stimulation was associated with greater stability, during all tasks, contrary to the sham condition. Significant improvement in area, velocity and acceleration, and jerkiness of sway, as denoted from IMU extracted parameters, was detected after active stimulation only.

What can be easily deduced from these studies is that cerebellar rTMS holds promise in tackling postural stability and speech impairment in PSP patients. However, the patient numbers remain small, and as such, bigger and better designed clinical trials are needed to confirm its efficacy and determine the most appropriate protocol.

*2.2. Motor Area Stimulation.* Motor cortex disinhibition has been shown to be a predominant feature in PSP pathology

[44]. RTMS has already been considered as a possible therapy method for parkinsonism in PD, and its therapeutic contribution to other similar disorders such as PSP is under investigation, especially regarding axial rigidity and falls, cardinal symptoms of PSP.

The first pilot study exploring the efficacy of rTMS application over the motor cortex in PSP patients was carried out by Santens et al. [37]. In this study, 6 PSP-RS patients were enrolled. The subjects received HF-rTMS (10 Hz, 80% of MT intensity) of 1000 pulses targeting the lower limb motor area for 5 consecutive days. Clinical evaluation was conducted at baseline and after the last stimulation on all patients, according to the Clinical PSP-RSc. The total score of PSP-RSc improved in five of the patients after the stimulation, with the most prominent effect shown on the gait/midline symptoms. A subjective improvement of overall function and mobility was reported from the subjects, albeit lasting for only 2-3 days. These findings suggest a potential benefit of rTMS in PSP patients, especially for gait and midline symptoms. Nevertheless, the validity of these results is questioned due to the small cohort and the absence of sham stimulation.

Nishida et al. [38] investigated the efficacy of rTMS in 6 PSP-RS cases and one PSP-pure akinesia with gait freezing (PSP-PAGF) patient. Evaluation at baseline and after the stimulation was carried out on all subjects via the PSP-RSc. Real HF-rTMS (5 Hz, 110% of RMT intensity) of 500 pulses over the supplementary motor area (SMA) was applied for 10 days. The 10 trains of each session were equally shared between the two hemispheres. The results showed that rTMS increased PSP-RSc scores by 7 points. However, only total PSP-RSc scores significantly improved, contrary to each subitem of the scale, which did not show a significant individual change. Sham controlled stimulation was not included in the trial, and as such, a placebo effect could not be excluded.

Major et al. [39] studied the effects of rTMS on the motor symptoms of a PSP patient using goniometry and dynamometry [39]. The case subject was a 65-year-old man with a dominant right hand. LF-rTMS (1 Hz, 80% of RMT intensity) was applied, with a 20 min duration per day, for five days consecutively, over the motor cortex bilaterally. Mechanography evaluation included a goniometer, recording the angles in 15 simple movements, and a dynamometer measuring muscle strength. A significant increase in range motion and muscle strength was reported after the stimulation.

Collectively, these studies show that rTMS over the motor areas can provide beneficial effects on motor symptoms in PSP patients. However, the small cohorts, the absence of sham stimulation control, and the possible placebo effect question the generalization of the reported results. Furthermore, trials including all PSP phenotypes (not only PSP-RS) should be conducted. The results are promising, but still, more trials are needed to evaluate their persistence and reproducibility. Additionally, evidence is stronger for HF-rTMS, but small-scale evidence of LF also being effective, such as the aforementioned case report, raise questions regarding the underlying mechanisms in PSP, and what researchers will need to target in the future, and how.

*2.3. Dorsolateral Prefrontal Cortex Stimulation.* Prefrontal cortex abnormalities are thought to be the pathophysiological source of depression in PSP patients [45]. Following this line of thought and based on the fact that rTMS over this area has received strong recommendation for treating major depression in the latest guidelines [50], Boulogne et al. [40] applied LF-rTMS (1 Hz, 120% of RMT intensity) targeting the right dorsolateral prefrontal cortex (DLPFC) of a 62-year-old PSP male patient with treatment-resistant major depression. The subject was neurologically and psychologically examined and evaluated using the PSP-RSc and the Montreal cognitive assessment (MoCA), along idea number of other psychiatric scales, namely, the State-Trait Anxiety Inventory (STAI), the Montgomery Asberg Depression Rating scale (MADRS), the Lille Apathy Rating Scale (LARS), and the Global Assessment of Functioning (GAF) Scale, all administered at baseline and after the rTMS intervention. Except for hydroxyzine administration upon serious anxiety symptoms, no other treatments were applied. The researchers observed an improvement in depressive symptoms and apathy after rTMS application; in greater detail, the MADS and STAI scores decreased, while the LARS and GAF scale scores increased after rTMS. This case study shows that rTMS over right DLPFC may relieve depression and contribute to a better life quality of PSP patients, though this remains a sole case report.

Regarding language impairments, Madden et al. [41] published a case report, indicating that stimulation targeting the left DLPFC in PSP patients can produce benefits regarding language functions. The technique of noninvasive stimulation of brain applied on the PSP patient was not TMS but transcranial direct current stimulation (tDCS). The subject studied was a male PSP patient with speech deficits such as declined verb fluency and speech production. A group of language exercises was used to evaluate the patient's language production at baseline and after sham or active application of tDCS targeting the left DLPFC. After each intervention, a different group of exercises was used to avoid any practice effect. This protocol was repeated four times, and the patient was blind to the stimulation status, real or sham. Comparison of speech production effects, between the groups of real and sham intervention, showed that the patient benefited from tDCS in phonemic fluency and action naming.

Taken together, these two cases insinuate that LF-rTMS targeting the right DLPFC can be safe and beneficial for PSP patients with major depression resisting treatment, and that noninvasive brain stimulation over left DLPFC in PSP patients can improve language deficits, although the case report applied tDCS.

## 3. Multiple System Atrophy (MSA)

*3.1. Cerebellar Stimulation.* MSA patients usually present with defective movement control, which stems from cerebellar dysfunction and damage in cerebellar neural pathways [51]. In the cerebellum-M1 circuit, the Purkinje cells inhibit the cerebellar dentate nuclei, which normally induce excitatory effects on M1 area via the ventral thalamus [52].

Degeneration and atrophy of the cerebellum in MSA means Purkinje cell loss, indicating a disinhibition of the dentate nucleus and its excitatory effect [53], becoming a target in rTMS studies.

Liu et al. [46] studied the therapeutic outcome of rTMS on controlling motor movements and spontaneous brain activity in MSA patients [46]. This study enrolled 9 subjects with MSA, who received daily sessions of HF-rTMS (5 Hz, 100% of RMT intensity) for 5 days. The stimulation coil targeted the M1 cortex bilaterally and the right and left lateral cerebellum sequentially. The Unified Multiple System Atrophy Rating Scale (UMSARS) was used for motor control assessment at baseline and within 3 days after the stimulation. Resting-state brain network activity was assessed via fMRI. After the rTMS sessions, improved motor control was found in 7 patients, compared to baseline. In addition, the resting-state complexity of the motor cortex showed an increase after stimulation in 6 patients. The researchers also noticed that the change in motor scores correlated with the change noted in motor network resting-state complexity. This study presented as rationale that multifocal interventions have provided beneficial results in the setting of PD and applied a combined intervention as well. However, whether the noted results stem from stimulation of the cerebellum or the motor cortex or both cannot be deduced from this study. Additionally, the interaction of the simultaneous stimulation needs to be assessed; one cannot exclude a possibility of the two stimulations counteracting each other and attenuating the improvement.

A TMS study by Celebi et al. [54] reported impairments in cognitive functions that correlated with short-latency afferent inhibition (SAI) in MSA patients. SAI is a neurophysiological tool that assesses motor cortex excitability modulation and also corresponds to the inhibition of brain cortex via the cholinergic system [22, 55]. With this background, Yildiz et al. [47] investigated the alteration of cerebellar-cortical interactions in MSA-C patients after cerebellar rTMS intervention. Twelve MSA-C patients, 5 AD patients, and 9 healthy controls entered the study. All subjects were cognitively evaluated with a series of neurophysiological tests. Attention and spatial working memory were evaluated with a simple computerized reaction time (RT) task. Six hundred pulses of LF-rTMS (1 Hz, 90% of RMT intensity) were applied, targeting the lateral cerebellum (ipsilateral to the side recording the motor evoked potential). The study included two different sessions in the same day. Firstly, RT and SAI were evaluated with simple TMS, while during the second session, rTMS was applied, and RT and SAI were reevaluated within 10 minutes from the stimulation. The study found that cerebellar rTMS provoked an important improvement in SAI deficits only in the MSA-C patients. Additionally, regarding the RT, there was a significant improvement in post-rTMS RT values of the MSA-C patients in contrast with the pre-rTMS RT values but not in the healthy control subjects. This study indicates that rTMS over the cerebellum influences SAI, inducing changes in cognitive functions, and may thus be a promising therapeutic approach for MSA patients.

In summary, the few available studies show that rTMS over the cerebellum acts on the abnormal cerebellar-cortical inhibitory neuronal connections of MSA patients. Different protocols with both high and low frequency cerebellar rTMS both seem to induce clinical improvement in MSA patients, which needs to be cleared in future studies, especially double blind studies with larger cohorts and patients with pure cerebellar syndromes. Additionally, assessing the duration of the positive effects also needs to be addressed, by including assessment sessions surpassing the initial week after the intervention.

*3.2. Motor Area Stimulation.* Chou et al. [48] conducted a double-blind, controlled with sham rTMS study assessing HF-rTMS over the left M1 in MSA. Twenty-one right-handed MSA patients were randomly categorized into a real or sham rTMS group. At baseline, all subjects were evaluated for their motor functions using the UMSARSII and received a resting-state fMRI. The rTMS intervention protocol included 10 HF-rTMS sessions (5 Hz, 110% of RTM intensity) of 1000 pulses targeting the left M1, over a span of 2 weeks, one session per day for five days in each week. After the 5th day of intervention, a midstimulation evaluation with the UMSARSII was conducted. At the end of all sessions, all patients received a resting-state fMRI and another UMSARSII assessment. The sham group followed the same protocol but with the coil positioned over the scalp with the back inactive surface. Motor symptoms were significantly improved (decreased UMSARSII) only in the real rTMS group. The resting-state fMRI data investigated differences between the real and sham rTMS application, before and after the rTMS intervention. A set of 47 functional connections was found to be significantly changed in the real rTMS group after the intervention. In addition, when examining the correlation of these brain link alterations and the motor symptoms improvement, a significant association for 10 of these connections was found. None of these correlations were reported for subjects that received sham intervention. This study suggests that HF-rTMS targeting the left M1 produces an improvement of motor symptoms by modulating specific brain functional connections.

The same team also conducted another study investigating the therapeutic outcome of rTMS targeting the left M1 of MSA patients [49]. They enrolled 15 right-handed MSA patients, 7 of which received the treatment and 8 consisted the controls. Additionally, a group of 18 healthy controls subjects, matched on age and sex, was prospectively included. At baseline, all MSA patients were assessed for their motor deficits, with the UMSARSII. The experimental procedure consisted of two fMRI sessions, before and after 10 sessions of HF-rTMS (5 Hz, 110% of RMT intensity) targeting the left M1, over 2 weeks, one session per day for 5 days per week. During fMRI scanning, a tapping exercise was performed. RTMS was not applied to the healthy controls, and fMRI examination was conducted only once. Patients in the sham group followed the same protocol but with the coil touching the scalp from the inactive back side. After the 5th rTMS session, a midstimulation evaluation with the UMSARSII was conducted. At the end of all

stimulations, all patients received a resting-state fMRI and a final motor assessment with the UMSARSII. After rTMS treatment, only patients receiving active stimulation showed significant improvements in their UMSARS-II scores and their motor impairment. Comparing the fMRI data between the healthy control group and the MSA group, a bilateral increase in cerebellar cortex activation was detected in the MSA patients. Comparison between the active and sham rTMS groups showed that the cerebellar activation was significantly higher after the real stimulation. This study indicates that HF-rTMS may improve the motor deficits, accompanied by an increased activation of the cerebellum after motor cortex stimulation.

Taken together, these results suggest that HF-rTMS targeting the left M1 probably leads to a significant improvement on motor dysfunction in MSA. Increased activation of the cerebellar cortex as shown with fMRI could correlate with the clinical improvement. However, double-blind studies with larger cohorts are needed, in order for these results to be confirmed and replicated.

## 4. Corticobasal Degeneration (CBD)

The only study investigating the therapeutic role of rTMS in CBS was conducted by Shehata et al. [56]. Twenty-six CBS patients were enrolled in the study and were followed for 12-18 months. A combination of rTMS, pharmacotherapy, rehabilitation therapy, and injection of botulinum toxin was applied. The akinetic-rigid syndrome and cognitive dysfunction were the predominant symptoms for the majority of the subjects. LF-rTMS (1 Hz, 90% of MT intensity) was applied to all patients targeting the contralateral motor cortex of the more damaged side, with one session, 3 times a week for 1 month, every 3 months. The subjects were assessed using a variety of clinical scales and were evaluated every 3 months. In short, after 3 months, the UPDRS, caregiver burden, and quality of life were improved, while cognitive functions remained stable, and this improvement was detected up to 18 months later. *T*he lack of control subjects and a possible placebo effect are the main limitations of the study, implying that more clinical trials, sham controlled, randomized, and double-blinded are necessary to elucidate the results of LF-rTMS or other forms of rTMS in CBS therapy.

## 5. Lewy Body Dementia (LBD)

Due to the similarities between LBD and PD and other dementias where rTMS has shown its potential, rTMS has long been insinuated as a possible therapeutic option for LBD [57]. However, there is only one trial assessing rTMS in LBD therapy, focusing on depressive symptoms. In this study, 6 LBD patients with drug-resistant depression were assessed after rTMS intervention. Daily sessions of LF-rTMS (1 Hz, 110% of MT intensity) targeting the right DLPFC and HF-rTMS (10 Hz, 100% of MT intensity) targeting the left DLPFC were applied for ten days. Hamilton Depression Scale (HAL-D) was used for evaluation at baseline and after the intervention showing a significant attenuation of depressive symptoms [58].

## 6. Ongoing Trials

Searching the clinicaltrials.gov website (last accessed on the 24th of November 2021) with the keywords "PSP" and "rTMS", we came up with 4 studies. Of these, the NCT02236832 study applies rTMS only on healthy participants as a control group and was thus not further read. A cross-over sham-controlled study (NCT04222218), lastly updated in January 2020,will apply cerebellar rTMS-theta burst to PSP patients, assessing its efficacy in postural instability using wearing sensor technology, and has been listed as completed since November 2019, though no results have been made available. Similarly, the NCT01174771 is also listed as complete since February 2012 and was lastly updated in May 2014. This pilot study investigates the potential benefits of the application of rTMS in PSP and CBD patients. This trial proposes that HF- and LF-rTMS targeting motor and prefrontal cortical regions in PSP and CBD patients respectively, may ameliorate motor and cognitive dysfunction; however, no results have been published yet. The NCT04468932, lastly updated in July 2020, investigates the effects of rTMS on motor control in PSP. This study is aimed at proving that cerebellar inhibition via cerebellar LF-rTMS will decrease postural instability in patients with PSP by increasing functional connectivity between the cerebellum, thalamus, and primary motor cortex.

Regarding the research for the studies using rTMS in MSA patients, 2 ongoing trials were found via our search. The NCT04595578, lastly updated in October 2020, applies a combination treatment with cerebellar rTMS and physical therapy (PT) in patients with MSA-C and spinocerebellar ataxia. This pilot study investigates the efficacy and the safety of the combined application of cerebellar rTMS and PT, contrary to the single PT therapy (sham rTMS intervention) in MSA-C patients. However, no results have been published yet. A randomized trial NCT04313530, lastly updated in March 2020, investigates the mechanism and effect of rTMS intervention in MSA patients with fatigue. The researchers' anticipation is that after rTMS there will be a decrease of fatigue in MSA patients, based on the hypothesis that fatigue in MSA may be associated with an altered default mode network and sensorimotor network connectivity.

## 7. Discussion and Conclusions

The majority of rTMS studies on parkinsonism focus on PD. This is reasonable considering the high frequency of this degenerative disease, but the small number of studies on atypical parkinsonian disorders (APDs) highlights the need for additional research regarding these diseases, as they also affect numerous individuals and may ultimately be more debilitating than PD, given the lack of effective treatments.

Regarding PSP, most studies indicated that cerebellar rTMS exerted positive effects, improving postural instability and speech impairment [34–36]. This could be the reflection

of improvement in cerebellar-brain inhibition, as Dale et al. [35] and Brusa et al. [34] even quantified and used as an outcome measure for their study, based on studies revealing its diminishing in the setting of PD and PSP [34, 35]. CBI is a physiological cortical inhibition by cerebellar Purkinje cells, crucial for proper motor control. TMS studies revealed that stimulation over the cerebellum recruits the cerebello-thalamo-cortical pathway and restores CBI [59], possibly explaining the amelioration of kinetic parameters shown in cerebellar rTMS studies in PSP. In fact, the study by Brusa et al. [34] showed that CBI was the only cerebellocortical functional connectivity index improved upon cerebellar rTMS. However, only one double-blinded study was available in this domain, so evidence is preliminary at best.

Furthermore, rTMS application over the motor area and the DLPFC showed beneficial effects in motor and depressive symptoms, respectively [38–40]. Nevertheless, several questions arise, which still remain unanswered. In almost all of the aforementioned studies, the PSP patient groups almost exclusively included the Richardson's syndrome subtype of PSP. The update of the clinical diagnostic criteria for PSP in 2017 emphasized the large phenotypical heterogeneity of PSP. Richardson's syndrome appears as only one type of the ten possible PSP phenotypes. There are no clinical trials examining the effect of rTMS on the rarer SP phenotypes. Only Nishida et al. included six patients with a different variant, the PSP-pure akinesia with gait freezing (PSP-PAGF). As such, more studies are needed, to evaluate the efficacy of rTMS to the whole phenotypical spectrum of PSP. Additionally, conflicting results have arisen due to both LF and HF protocols giving positive results. Regarding the motor symptoms, reduced intracortical inhibition has been highlighted as a feature of PSP [44], so LF protocols, which induce inhibitory changes, may hold more meaning to be explored in the future. Besides, the two studies that applied HF-rTMS and reported positive results [34, 35] showed that these were either short-lasting or insignificant in the various subitems. Finally, Madden et al. [41] reported a case of tDCS improving language deficits in a PSP patient. Albeit not rTMS, this study is important in bringing forward the potential of noninvasive brain stimulation as an effective modality in neurodegenerative diseases and PSP in particular.

The rTMS studies regarding the cerebellum in MSA have not aided in pinpointing a certain direction this far. The few available studies have been vastly heterogeneous, and regarding the cerebellum, both LF and HF protocols over the same area seem to be beneficial, one regarding motor and the other cognitive performance [47, 60]. This seems heavily counterintuitive and further raises questions of erroneous methods in the studies. In MSA, the cerebellum seems to be affected in a way that is similar to PSP; reduced physiological cerebellar inhibitory inputs give way to motor disorders. In this sense, HF protocols, increasing this input, should be able to present better results, as shown in the study addressing motor deficits. The reasons behind LF-protocol seemingly producing cognitive benefits remain unclear; it could be the case that different circuits are involved in each pathology but without further studies to counter or corroborate the aforementioned results; one cannot reach any conclusions. On the contrary, the results of two sham-controlled studies involving the left motor cortex have provided consistent positive results, with implication of the cerebellum as well [48, 61]. However, both of them were conducted by the same group and were not double-blinded.

The search for studies on rTMS and CBD or LBD yielded only two trials involving patients of these degenerative disorders. First, Shehata et al. [56] studied the efficacy of LF-rTMS to twenty-six CBS patients. According to their results, many disease parameters were improved after three months, and the improvement was maintained for more than a year postintervention. The rationale of this study in applying LF-rTMS lay in studies showing reduced cortical inhibition in LBD and in previous studies of rTMS over the motor cortex of PD patients yielding positive results. This train of thought is useful, in drawing inspiration for the already lain road of PD, and more studies in this direction are more than encouraged.

Of note, this is the only study in the mentioned literature that followed the patients for 18 months and could draw conclusions on the long-term results of the intervention. The duration and the persistence of the beneficial effects of a therapeutic intervention are of major importance when assessing a therapeutic option, and more research is needed regarding near-transfer effects of rTMS in APDs and the longitudinal observation of possible rTMS benefits. It will be even more interesting to see whether rTMS is even capable of slowing the progression of some of these diseases and gain a preventative, rather than a solely therapeutic role.

Future studies should address some issues mostly concerning the study design. Large studies with big cohorts are not easy to be organized, as a lack of equipment and qualified research staff is often encountered. A multicenter study design could gather larger samples of patients, and consequently, more accurate results could be obtained. Sham-controlled studies must be preferred, so that the placebo effect may be controlled for. Some of the mentioned trials did not apply sham stimulation, driving to a lower quality of their study. Dale et al. [35], who investigated cerebellar rTMS effects in two PSP patients, used sham stimulation, though a different sham stimulation was applied on each of the patients. One of them could understand the sham intervention since this superficial stimulation could not produce the same sensation over the head and neck area as the real one. Naturally, this placebo effect raises doubts on the trial findings and highlights the need for proper methodology.

The application of rTMS in earlier disease stages is another issue that needs to be discussed. For instance, regarding AD, a common degenerative disorder combined with dementia, the excitant literature shows that patients in earlier stages had responded better after treatment with rTMS [32, 62, 63]. This phenomenon could be explained from the smaller degree of brain atrophy, contributing to better responsiveness to rTMS [64]. An early diagnosis of APDs would enable the earlier application of rTMS with probably better modulation effects, but the great variety of phenotypical expression of these disorders and their lower prevalence contribute to a difficult early differential

diagnosis. Nowadays, there are important scientific attempts towards reaching an accurate and early diagnosis of APDs, using updated clinical criteria, functional imaging, and nuclear medicine. As such, future trials could attempt to assess the effect of rTMS therapy on early stages of these disorders or compare its efficacy between earlier and more advanced stages.

In conclusion, particularly because of the limited pharmacologic and nonpharmacologic treatment options for patients with APDs, rTMS is a promising tool for therapy. However, the determination of the exact therapeutic protocols still has a long way to go due to the lack of large-scale trials, driving to the urgent need of high quality clinical studies, providing strong evidence on the persistence and reproducibility of the observed beneficial effects.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Hindawi
Behavioural Neurology
Volume 2021, Article ID 9164543, 14 pages
https://doi.org/10.1155/2021/9164543

*Research Article*

# Transcranial Magnetic Stimulation and Working Memory Training to Address Language Impairments in Aphasia: A Case Study

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Received 15 July 2021; Revised 25 October 2021; Accepted 10 November 2021; Published 25 November 2021

Academic Editor: Enzo Emanuele



*Background.* Traditionally, people with aphasia (PWA) are treated with impairment-based language therapy to improve receptive and expressive language skills. In addition to language deficits, PWA are often affected by some level of working memory (WM) impairments. Both language and working memory impairments combined have a negative impact on PWA's quality of life. The aim of this study was to investigate whether the application of intermittent theta-burst stimulation (iTBS) combined with computerized WM training will result in near-ransfer effects (i.e., trained WM) and far-transfer effects (i.e., untrained language tasks) and have a positive effect on the quality of life of PWA. *Methods.* The participant was a 63-year-old Greek-Cypriot male who presented with mild receptive aphasia and short-term memory difficulties. Treatment was carried out using a multiple baseline (MB) design composed of a pretherapy or baseline testing phase, a therapy phase, and a posttherapy/follow-up phase. The treatment program involved iTBS application to the left dorsolateral prefrontal cortex (DLPFC), an area responsible for WM, for 10 consecutive sessions. The participant received a 3-minute iTBS application followed by 30-minute computer-assisted WM training. Outcome measures included a WM screening test, a standardized aphasia test, a nonverbal intelligence test, story-telling speech samples, a procedural discourse task, and a questionnaire addressing quality of life. These measures were performed three times before the treatment, immediately upon completion of the treatment, and once during follow-up testing at 3 months posttreatment. *Results.* We found a beneficial effect of iTBS and WM training on naming, reading, WM, reasoning, narrative, communication efficiency, and quality of life (QoL). *Implications for Rehabilitation.* Noninvasive brain stimulation combined with computerized WM training may be used in aphasia rehabilitation to improve WM and generalize to language improvement.

## 1. Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive technique of brain neuromodulation and neurostimulation [1] which produces a brief electric current in the coil to generate a magnetic field, and in turn, it activates neurons in the vicinity of the coil. Recently, there is a growing interest in the area of working memory (WM) improvement through the use of TMS [2]. WM, the ability to temporarily store and manipulate information in the provision of ongoing tasks, is based on the belief that a dedicated system maintains and stores information in the short term and that this system underlies human thought processes [3]. While a range of cognitive abilities has been associated with WM, including reading comprehension, logical thinking, general intelligence, learning ability, and fluid reasoning [4–8], recent investigations explore how cognitive enhancement can support improvements in other areas (i.e., language) in people with neurological impairments [9, 10].

Aphasia has traditionally been defined as a language impairment due to the disruption of the blood flow to the brain, which can result in reduced ability to comprehend and/or express oral and/or written language. Lately, research studies investigate whether aphasia is the result of a cognitive

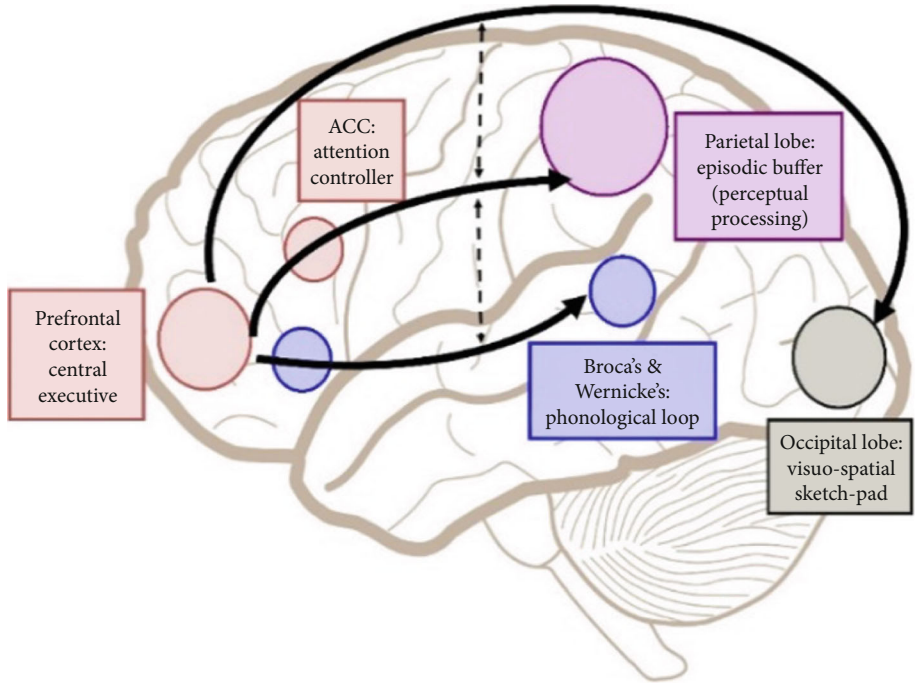


Figure 1: The multicomponent working memory model (Baddeley, 2010) represented simplified as implicated in the brain, in which the central executive assumes the role to exert control and oversee the manipulation of incoming information for intended execution. ACC: anterior cingulate cortex. From Working Memory from the Psychological and Neurosciences Perspectives: A Review by Chai et al., 2018, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5881171/figure/F1/Copyright© 2018 Chai, Abd Hamid and Abdullah.

process disruption, specifically the disruption of the WM neural network [10]. In the recent past, aphasia was also defined as a cognitive disorder with major linguistic deficits, as opposed to a specific language disturbance [11]. This notion is based on evidence indicating the possible breakdown of an underlying neuronal mechanism that corresponds to a network consisting of several cortices interconnected by white matter tracts [11]. Interestingly, many studies have identified the WM neural network at the frontoparietal area, involving the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC), and the parietal cortex (PAR) [12–15]. More precisely, the DLPFC has been implicated mainly in tasks demanding executive control such as those requiring integration of information for decision-making, maintenance and manipulation/retrieval of information, and information updating [12]. Chai et al. [16] provided a visual interpretation of Baddeley's theoretical formulation of the multicomponent WM model [17] to specific regions in the human brain as depicted in Figure 1 below. The DLPFC is known for its involvement in WM tasks and for its significant contribution to tasks accuracy [18, 19]. Previous studies have provided evidence of increased activation of the DLPFC during WM tasks [20–22]. In order to achieve a cognitive target such as WM training, WM simultaneously participates in information processing and storage [8]. When WM fails, the ability to carry out many activities of daily living is reduced [23]. Due to this involvement in multiple WM components, the DLPFC is a desirable target for neuromodulation in the context of WM training.

Previous studies have suggested that the neural systems underlying WM capability is plastic, and therefore, WM updating training can lead to WM improvement, particularly in individuals with WM deficiencies [24–26]. Additionally, the effects of training can be transferred to other cognitive functions associated with WM such as general fluid intelligence (Gf) [27]. Gf is defined as the ability to solve novel reasoning problems, and it is associated with comprehension, problem solving, and learning [28]. Gf is a complex ability that enables an individual to adapt their thinking to new cognitive problems and situations [27], and it has been identified to share the same neural networks in the lateral prefrontal and parietal cortices as WM capability [8, 27, 29].

This current study supports that when a stroke occurs, the WM neuronal network is disrupted, resulting in aphasia. The main objective was to explore the potential domains of transfer effect after stimulation of the left DLPFC and WM training and also to measure how efficacious this treatment protocol was for PWA. Specifically, the purpose was to investigate the short-term and long-term combined effects of iTBS and WM training as a mediator to WM improvement, language generalization, and to quality of life (QoL) enhancement. Cognitive (nonverbal), language (verbal), and QoL outcomes are reported at pretherapy (baseline), posttherapy (immediately after the end of the treatment), and follow-up (three months posttreatment).

## 2. Materials and Methods

*2.1. Inclusion and Exclusion Criteria.* The study was carried out at the Rehabilitation Clinic of the Cyprus University of Technology (CUT). Inclusion and exclusion criteria to the

Table 1: Participant inclusion and exclusion criteria.

| Inclusion criteria | Exclusion criteria |
|---|---|
| (a) Native speaker of Cypriot-Greek | (a) Severe aphasia diagnosed using the Greek version of the Boston Diagnostic Aphasia Examination – Short Form (BDAE-SF) [30] |
| (b) Age 21-79 y.o | (b) Damaged dorsolateral prefrontal cortex area as identified in the MRI |
| (c) First-time single left hemisphere stroke | (c) Traumatic brain injury |
| (d) Presence of aphasia | (d) History of psychiatric or other neurological illness |
| (e) Right-hand dominance | (e) Depression |
| | (f) Epilepsy/seizures |
| | (g) Pregnancy |
| | (h) Colour-blindness or other visual disorders/visual neglect |
| (g) Adequate single-word comprehension | (i) Hearing loss |
| | (k) Significant general medical problems including liver, cardiac, or renal dysfunctions |
| | (l) Present or past alcohol or drug abuse |
| | (j) Metal or medical implants (i.e., cardiac pacemakers) |

study were made available prior to entering the study (Table 1).

The study was approved by the Cyprus National Bioethics Committee, and the participant provided a written consent prior to participating in this study.

*2.2. Participant Details.* The participant (C.S.) was a 63-year-old male who suffered a left hemisphere ischemic stroke 45 days prior to the study and was not receiving speech and language therapy. C.S.'s neurologist stated that he experienced mild expressive aphasia with short-term memory (STM) difficulties and verbal information processing difficulties. C.S.'s reported having difficulties remembering recent verbal information while having a conversation with family and friends. He was a retired food and beverage employee, with 12 years of education, and was a hobby farmer. Although brain damage was not visible on the current MRI (Figure 2), the initial medical MRI report indicated the presence of an acute ischemic stroke in the medial temporal lobe. C.S. lived with his wife and did not suffer any paresis or paralysis as he was able to drive and care for himself with minimal assistance.

*2.3. Data Collection and Procedures.* The assessment battery was administered in a predetermined order in 2 sessions, of approximately 2.5 hours duration in total.

*2.3.1. Background Tools.* The background tools were used to fulfil certain inclusion criteria in order to proceed to the pretesting and treatment stage of this study. A detailed case history was taken including personal and medical information. A TMS safety questionnaire [31] was completed prior to entering the first stage of the inclusion process, followed by a screening procedure which included the following:

(i) The *Albert's Visual Neglect Test* [32] to determine unilateral spatial neglect

(ii) The *Edinburgh Handedness Inventory* [33] aimed at evaluating handedness of the preferred hand for carrying out daily activities

(iii) The Greek adaptation of the *Beck's Depression Inventory-II* [34, 35], to measure characteristic attitudes and symptoms of depression

*2.3.2. Assessment Tools.* A battery of tools was administered at baseline, immediately after treatment (same day), and 3 months posttreatment at the follow-up stage. The tools used were as follows:

(i) The *Raven's Coloured Progressive Matrices* (RCPM) [36]

(ii) Subtests from the Greek version of *Boston Diagnostic Aphasia Evaluation–Short Form* (BDAE-SF) [30]

(iii) The *RehaCom Working Memory Screening Task*

(iv) A *personal stroke narrative* [37]

(v) The *Multilingual Assessment Instrument for Narratives* (MAIN) [38]

(vi) A *Procedural Discourse* task [39]

(vii) The *Stroke and Aphasia Quality of Life Scale-39* (SAQOL-39) [40]

The RCPM [36], a test used to measure abstract reasoning, is also regarded as a nonverbal estimate of Gf [41]. The RCPM is made up of a series of diagrams or designs with a part missing, and the participant is asked to choose the shape to complete the pattern or shape from six alternatives. The Greek version of RCPM was administered as adapted by [42]. Every correctly solved pattern was given 1 point, with a total score range between 0 and 36 [43].

The *BDAE-SF* [30] has been standardized in Greek and is culturally appropriate [44]. It includes five subtests:

(1) Conversational and expository speech such as simple social responses, free conversation, and picture description

(2) Auditory comprehension including word comprehension, commands, and complex ideational material

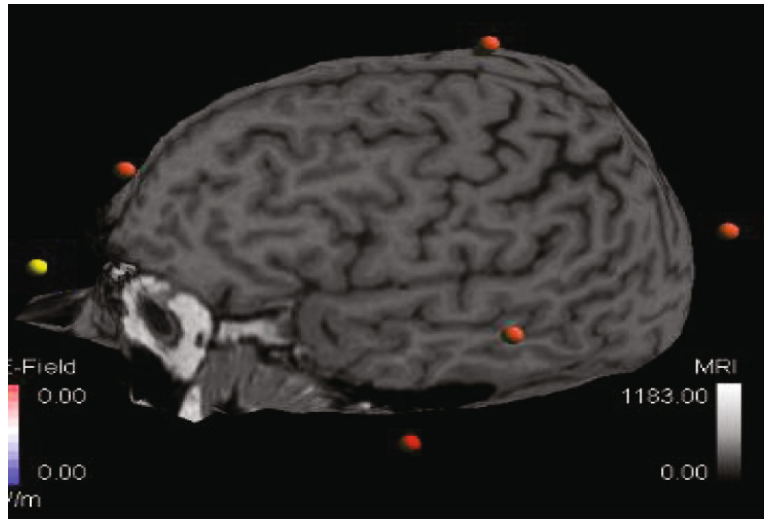


Figure 2: Reported findings of the current MRI noted two small areas of low signal intensity involving the subcortical white matter of the left occipital lobe and the left temporal lobe which were compatible with small areas of brain parenchymal loss.

(3) Oral expression, such as automatized sequences, single word repetitions, repetitions of sentences, responsive naming, the Boston Naming Test–Short Form (BNT-SF), and screening of special categories

(4) Reading, including letter and number recognition, picture-word matching, basic oral word reading, oral reading of sentences with comprehension, and reading comprehension of sentences and paragraphs

(5) Writing, including mechanics, dictation writing of primer words, regular phonics and common irregular forms, written naming, narrative writing mechanics, written vocabulary access, syntax, and adequacy of content

For the purposes of this study, only subtests 1-4 were administered and results were analysed in accordance with the test manual.

The *RehaCom Working Memory Screening* module is a tool used to assess both simple WM span (simple information holding) and the retention and processing of visual-spatial information. When the WM screening task is initiated, ten dots are presented in a circular arrangement. Individual dots sequentially turn red and fade. The first sequence consists of two random dots out of the ten lighting up in a particular order to be repeated correctly. When selected correctly, the number of dots increases in the next sequence. In sum, the task is to memorize the presented sequence of dots lighting up. The WM screening subtest ends after two consecutive incorrect sequence responses or after 7 minutes. The visual-spatial memory span is measured by the maximum length of the memorized dot patterns that can be reproduced immediately without errors. Additionally, the participant's memory span is calculated based on the highest sequence length measured in number of dots, reproduced without mistakes in position and order, and it is confirmed by completing two consecutive sequences with the same number of dots.

A *personal stroke narrative* was elicited by asking the participant to describe how his stroke occurred [37]. The sample was transcribed and analysed using the *Shewan Spontaneous Language Analysis* (SSLA) system [45] in accordance with the SSLA protocol. Variables for analysis included number of utterances, time (total speaking time in minutes), rate (syllables per minute), length (percentage of utterances $\leq 5$ words), melody, articulation, complex sentences (percentage of utterances that contained one independent clause and one or more dependent clauses), errors (percentage of grammatical, syntactic, or morphological errors), content units (units that conveyed information), paraphasias (percentage of substitutions), repetitions, and communication efficiency (content units/time).

The *MAIN* [38] is a tool designed to evaluate narrative tell and retell skills in children but has also been used with adults with acquired language deficits associated with neurological disease for research purposes [46]. The MAIN stories consist of coloured picture sequences developed according to strict psycholinguistic criteria. While the MAIN examines narrative production at microstructure and macrostructure levels, for this study, only the macrostructure of the generated story was analysed. The primary unit for macrostructure analysis is the episode. The content of each picture sequence was designed to represent three short episodes. Each episode consists of

(i) a goal statement for the protagonist

(ii) an attempt by the protagonist to reach the goal

(iii) an outcome of the attempt in terms of the goal

(iv) the internal states (IST) which initiate the goal and also express reactions

Each story is controlled for cognitive and linguistic complexity [38] and has a moral meaning similar to an Aesop

fable. In this study, the "Baby Goats" story was used which portrayed a mother goat wanting to save her baby goat who jumped into the water but a fox jumped forward to catch the other baby goat. Then, a bird saw that the baby goat was in great danger and stopped the fox by biting its tail and chasing it away to save the baby goat. Six-coloured pictures in the form of a cartoon strip were presented, and one-episode was unfolded each time (2 pictures) for the participant to narrate a story based on the pictured stimuli. The scoring sheets of the MAIN "Baby Goats" story provided the scoring system used for the story structure components (setting, goals, attempts, outcomes, and IST). A setting statement, which gives time and place and introduces the story's protagonist, is scored with zero points for wrong or no response, 1 point for one correct response, and 2 points for reference to both time and place. This component is followed by three episodes. Each episode consists of (a) the internal states which initiate the goal and also express reactions; (b) a goal which is a statement of an idea of the protagonist to deal with the initiating event; (c) an attempt by the protagonist to reach the goal, which is an indication of action to obtain the goal; (d) an outcome of the attempt in terms of the goal, which is the event(s) following the attempt and causally linked to it; and (e) the internal states as reaction, which is a statement defining how the protagonist(s) feel or think about the outcome or an action resulting from an emotional response [38]. The story output was transcribed verbatim, and it was analysed using a scoring system of 17 points for story structure components in production, following the guidelines for assessment, and guided by the information on the provided scoring sheets.

The *Procedural Discourse* task is considered a semispontaneous speech production task that assesses discourse ability following the main concept analysis (MCA) procedure [39]. The MCA enumerates the speaker's ability to communicate the overall idea of an occasion, and it provides a way to evaluate the generated precision and completeness of the critical concepts of the shared topic. The participant was instructed to verbally provide all the required steps to be taken in order to prepare a sandwich. The generated language sample was analysed using the MCA procedure referring to the ten main concepts. The total number of main concepts expected to be produced was analysed and measured based on the concept content as listed below:

(1) Get the bread out

(2) Get two slices of bread//halved bread

(3) Get the butter

(4) Get the (rest of the ingredients, i.e., ham and cheese)

(5) Get a knife

(6) Put/place the bread on the plate

(7) Put/spread butter on bread

(8) Put the ingredients (i.e., ham and cheese) on bread

(9) Put the two pieces together

(10) Cut the sandwich in pieces

The first five steps comprise concepts concerning retrieving the ingredients needed, the following four steps include concepts concerning ingredient assembly, and the final concept describes the final appearance of the target (sandwich) prior to serving it. The procedure output was transcribed verbatim, and it was analysed using a binary scoring system of "1" for correct information and "0" for incorrect/missing information.

The *SAQOL-39*g has been translated and culturally adapted in Greek for use in Greece with PWA [47]. The Greek SAQOL-39g shows good reliability and validity [48] as a measure of health-related quality of life in people with stroke, including those with aphasia. An interview with the participant and the first author took place prior to the therapy study where the SAQOL-39 was used to collect the relevant information.

*2.4. Therapy Procedure.* The participant completed ten (10) approximately 45-minute-long treatment sessions comprising of iTBS, immediately followed by RehaCom WM training over a span of 10 consecutive days, including weekends. Within each treatment session, approximately 15 minutes were devoted for setting up the participant with the TMS equipment and iTBS application, and 30 minutes were devoted to the RehaCom WM training task. The treatment regimen is depicted in Figure 3 below.

*2.4.1. Pretherapy or "Baseline" Testing Phase.* During the pretherapy baseline phase, the purpose was to establish the level of performance prior to treatment so that the effects of treatment on the task could be clearly measured. Seven outcome measures were used, and the information was collected three times, one week apart, prior to the therapy phase. Preceding the therapy phase, a T1-weighted MRI image was obtained of C. S.'s brain in order to accurately locate the target stimulation site using the Visor 2.0 neuronavigation system (ANT NEURO). Neuronavigated positioning of the stimulation coil allowed for repeated accuracy throughout the study.

*(1) Transcranial Magnetic Stimulation (TMS) Equipment.* Single-pulse TMS and intermittent theta-burst stimulation (iTBS) were delivered over the motor cortex and the left dorsolateral prefrontal cortex (LDLPFC), respectively, with the Magstim Rapid2® stimulator (Magstim Co., Wales, UK) connected to a 70 mm figure-8 air cooled coil. Biphasic TMS pulses were delivered with a posterior-to-anterior (P-A) current direction in both, single-pulse TMS and iTBS. The treatment intensity of TMS was individually adjusted the participant's resting motor threshold (RMT). RMT is the minimal intensity at which TMS of motor cortex produces a reliable motor evoked potential (MEP) of minimal amplitude in the target muscle. The MEP was determined with a surface electromyography (EMG) response in the 'target' muscle, through the placement of EMG leads over the first dorsal interosseous (FDI) muscle of the left hand. Full

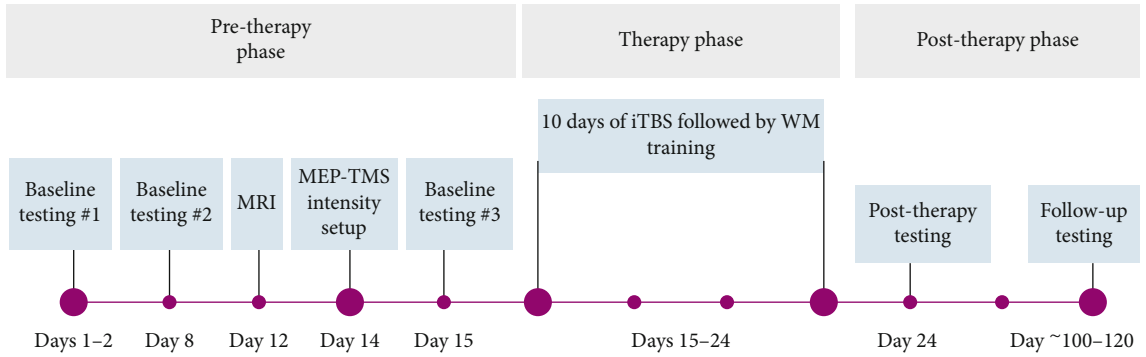


Figure 3: Study design overview.

muscle relaxation was maintained through visual and online EMG monitoring. The coil was positioned at 45-degree rotation in relation to the parasagittal plane to induce P-A current in the underlying cortex. The motor "hotspot" was determined with a TMS intensity ranging from 45% to 50% of the maximum stimulator output, whereby single-pulse stimuli were delivered at varying positions across the scalp near the primary motor cortex (M1) while guided by a neuronavigation system (ANT NEURO) using each participant's recent anatomical MRI image. The motor "hotspot" was determined as the position on the scalp that yielded two consecutive MEPs with greater amplitude than the surrounding positions. The location within the left motor cortex that consistently elicited MEPs in the relaxed right FDI muscle was then defined as the motor hotspot. The coil was then placed over the defined target to obtain a MEP in the FDI of at least 50 $\mu$V in five or more of 10 consecutive stimulations of the left hand [49]. For this study, a computerized adaptive parameter estimation through sequential testing (PEST) [50] with the software TMS Motor Threshold Assessment Tool, MTAT 2.0, developed by Awiszus and Borckardt et al. [50], was used to determine the RMT. The MTAT 2.0 freeware was obtained online (http://www.clinicalresearcher.org/software.html), and the option for assessment without prior information was selected. No other parameters were changed on the software.

#### 2.4.2. Therapy Phase

*(1) Transcranial Magnetic Stimulation: iTBS Application.* The figure-8 coil was positioned tangentially to the skull, with the handle parallel to the sagittal axis pointing occipitally. The iTBS treatment consisted of bursts of three pulses at 50 Hz given every 200 milliseconds in two second trains, repeated every 10 seconds over 200 seconds for a total of 600 pulses [51]. Based on the participant's recent MRI images, the Visor 2.0 neuronavigation suite (ANT-Neuro, Enschede, Netherlands) was used for image preprocessing, tissue segmentation, and registration into standard stereotaxic space. The stimulation target was defined in the left DLPFC by using the Talairach coordinates $x = -39$, $y = 34$, and $z = 27$ [21, 52]. This technology enabled the reliable three-dimensionally precise reapplication of rTMS throughout the study. The participant received one session of iTBS each day for 10 consecutive days.

*(2) RehaCom WM Training Equipment.* Immediately following the iTBS session, the participant received 30 minutes WM training using the RehaCom Working Memory (WOME) software package (Hasomed GmbH, DE.). RehaCom WOME is a software package developed to train and improve WM performance. The WM training task involved card presentation in the form of a card game, using a complete card deck of 52 cards and consisting of different levels of difficulty. Three hierarchically ordered modules were designed to exercise the main components of WM on the basis of a card game: (a) storage systems, involving the maintenance of information; (b) selective attention, involving memorizing selective parts of information and inhibiting others; and (c) central executive/manipulation processes, involving active operating with the content retained in WM [53]. RehaCom WOME training involves the memorization and manipulation of an increasing number of visually presented playing cards on a computer screen. Throughout the early levels of training, the participant is required to memorize a short series of cards and reproduce it in the same order, while at higher levels additional tasks are introduced to influence the memory process (e.g., memorize only the cards of a certain suit from a presentation of various cards). In total, there are 70 levels of difficulty. Feedback is constantly provided by the software, and the degree of difficulty is adapted based on the participant's performance level. The sessions were implemented in a quiet room, and C.S. responded on a Lenovo touchscreen laptop.

*2.5. Posttherapy/Follow-Up Phase.* The posttherapy/follow-up phase consisted of two time points. The outcome measures were administered immediately after the completion of the last day of treatment ($10^{th}$ day) and at 3 months post-treatment at the follow-up stage. The purpose of immediate posttesting was to determine short-term efficacy and of the follow-up to determine long-term effects. The exact date of the follow-up was dependent on the participant's availability when contacted to set-up the appointment. The same battery of tools was used as with the baseline phase:

(1) The Greek BDAE-SF [30]

(2) The RCPM [42]

(3) The MAIN [38]

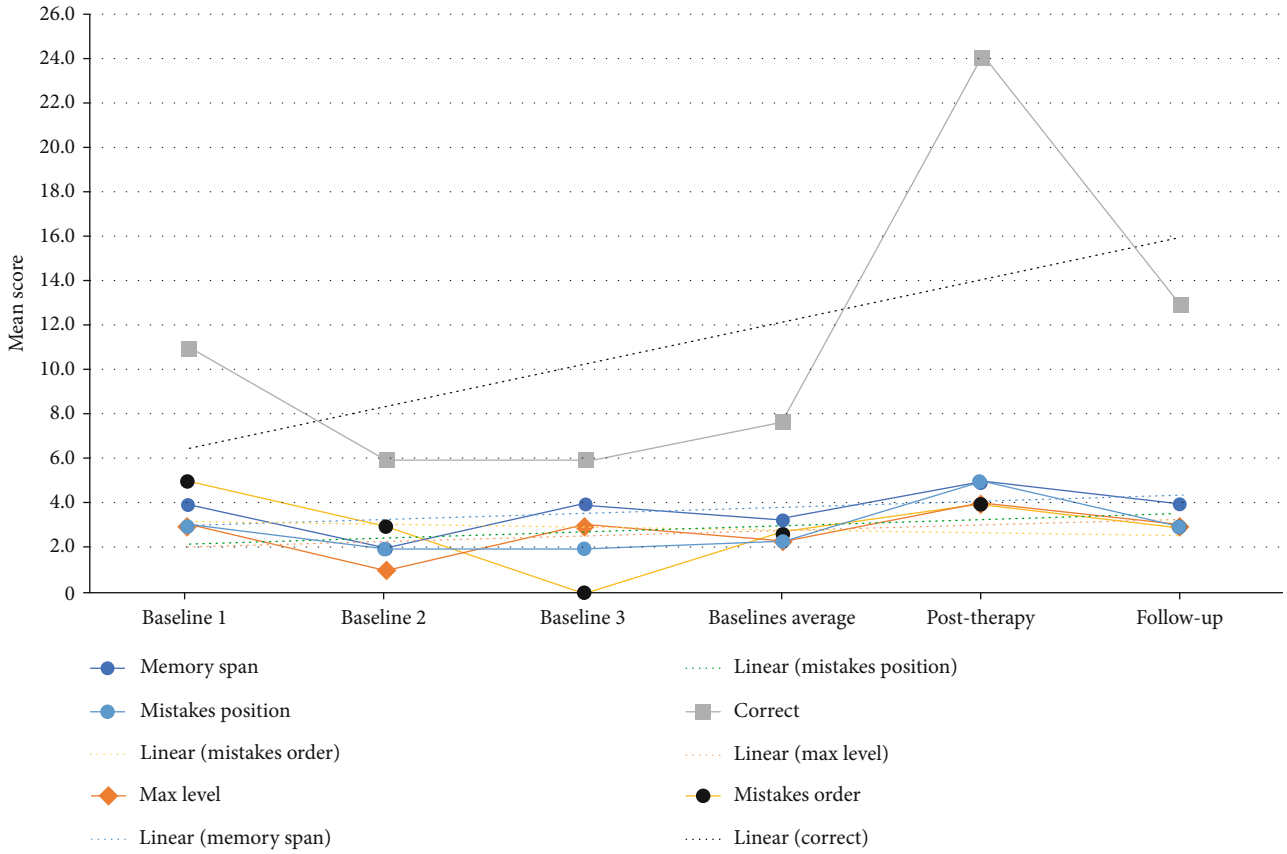


Figure 4: Schematic representation of C.S.'s raw scores on the *RehaCom* WM screening task.

(4) A Procedural Discourse task [39]

(5) A personal stroke narrative [37]

(6) The RehaCom Working Memory Screening Task

(7) The Greek SAQOL-39 [48]

## 3. Results

The Statistical Package for Social Sciences (IBM SPSS 25) was used for all the data and exploratory analysis. Analyses of individual data were conducted using the weighted statistics (WEST) method, and descriptive results' analysis was used where a statistical analysis was not suitable. Specifically, the "WEST-Trend" and "WEST-ROC" (one tailed) procedures [54] were applied. In order to evaluate the treatment effects and the rate of change, the level of performance prior to treatment is established by taking at least two probes [54]. A linear trend in improvement may be documented using the WEST-Trend procedure, while the amount of change in the treated (short-term) versus the untreated periods (long-term) may be documented using the WEST-ROC analyses. The WEST-ROC and WEST-Trend were used to analyse the data from the Greek BDAE-SF, the RCPM, the MAIN, and the Procedural Discourse. Results from the SSLA, the RehaCom WM screening, and the SAQOL-39g assessments are reported but a statistical analysis was not performed.

*3.1. Near-Transfer Effects of iTBS to the LDLPFC Combined with WM Training.* The results of the *RehaCom WM* screening show a positive linear trend (Figure 4) on all the tasks assessed with a more prominent trend for improvement in the correct responses task. The baseline average (avg.) was compared to the posttherapy and follow-up results (Table 2).

C.S. did not show an overall significant improvement in the RCPM results. However, a statistically significant trend for improvement was shown in *Subtest AB*, ($t(11) = 1.82$, $p = 0.048$) but the WEST-ROC showed that the difference between the treated and untreated periods was nonsignificant ($t(11) = 0.64$, $p = 0.268$). Results are shown in percentage correct in Table 3.

*3.2. Far-Transfer Effects in PWA of iTBS to the LDLPFC Combined with WM Training.* To investigate whether TMS and WM training generalized to untrained receptive and expressive language and functional communication tasks, statistical analysis was performed on results from (i) the *BDAE-SF*, (ii) the *Procedural Discourse* task, and (iii) the *MAIN* telling task (Table 4). The personal stroke narrative was analysed using the SSLA.

(i) Statistical analysis of the *BDAE* subtests revealed a significant overall trend for improvement only for the *Boston Naming Test* ($t(14) = 1.82$, $p = 0.045$) while the difference between the treated and

Table 2: *RehaCom* WM screening raw scores by the subcategory and study phase.

| | Baseline 1 | Baseline 2 | Baseline 3 | Baseline average | Posttherapy | Follow-up |
|---|---|---|---|---|---|---|
| Memory span | 4 | 2 | 4 | 3 | 5 | 4 |
| Max level | 3 | 1 | 3 | 2 | 4 | 3 |
| Correct | 11 | 6 | 6 | 8 | 24 | 13 |
| Mistakes order | 5 | 3 | 0 | 3 | 4 | 3 |
| Mistakes position | 3 | 2 | 2 | 2 | 5 | 3 |

Table 3: Raw scores (% correct) on the nonverbal intelligence outcomes at posttreatment and follow-up compared to the baseline for C.S.

| | Baseline 1 | Baseline 2 | Baseline 3 | Posttherapy | Follow-up |
|---|---|---|---|---|---|
| Mean RCPM | 75.00% | 69.44% | 72.22% | 77.78% | 77.78% |
| Subtest A | 83.33% | 75.00% | 75.00% | 83.33% | 75.00% |
| Subtest AB | 83.33% | 83.33% | 83.33% | 91.67% | 100.00% |
| Subtest B | 58.33% | 50.00% | 58.33% | 58.33% | 58.33% |

Table 4: Raw scores (% correct) on the language outcomes at posttreatment and follow-up compared to baseline for C.S.

| | Baseline 1 | Baseline 2 | Baseline 3 | Posttherapy | Follow-up |
|---|---|---|---|---|---|
| Boston naming test | 66.67% | 73.33% | 73.33% | 80.00% | 86.67% |
| BDAE reading subtest | 86.94% | 90.28% | 90.28% | 90.28% | 94.44% |
| Language discourse—MAIN | 47.06% | 47.06% | 47.06% | 58.82% | 64.71% |

untreated periods was nonsignificant ($t(14) = 0.27$, $p = 0.396$)

(ii) Statistical analysis of the participant's *BDAE Reading* subtest showed a significant trend for improvement ($t(6) = 2.00$, $p = 0.046$), but difference was nonsignificant between the treated and untreated periods ($t(6) = 0.30$, $p = 0.389$)

(iii) Statistical analysis of the participant's *Procedural Discourse* task showed that there were no differences in the number of responses between the five periods

(iv) There was an overall trend for improvement on the *MAIN*, but this did not reach significance ($t(16) = 1.37$, $p = 0.095$), as well as between the treated and untreated periods ($t(16) = 1.24$, $p = 0.116$). Improvement was noted for (a) the IST event as initiating of the second episode during posttherapy and follow-up, (b) the IST event as initiating of the third episode during posttherapy and follow-up, and (c) and IST as reaction of the second episode during follow-up

(v) C.S.'s stroke narrative (spontaneous language sample) was analysed using the SSLA protocol [45] which is designed to describe and quantify connected speech. The baseline average (avg) was compared with the posttesting and follow-up results. There was a 1% increase in the number of utterances produced between baseline avg and posttherapy and a 7% increase between baseline avg and follow-up. The rate of speech improved from 116.76 syllables per minute to 141.60 at posttherapy and to 152.22 at follow-up. The sentence length, which reflects the use of more than 5 words in the produced utterances, improved by 22% between baseline avg and follow-up. A 7% improvement was noted in sentence complexity between baseline avg and follow-up. Improvement was also noted between baseline avg and follow-up in the with an 11% reduction of errors. The number of content units improved from 19.33 at baseline avg to 21.00 at posttherapy and to 36.00 at follow-up. Improvement in the number of repetitions was noted with a reduction from 7% to 0% between baseline avg and posttherapy. A notable improvement in communication efficiency which reflects the rate at which information is conveyed by the speaker (number of content units divided by time), from 13.33 at baseline avg to 16.80 posttherapy and to 17.73 at follow-up. No paraphasias were produced in any of the stroke narrative samples, and the overall melody and articulation were judged to be normal (Table 5).

*3.3. Quality of Life Effects in PWA of iTBS to the LDLPFC Combined with WM Training.* With regard to investigating whether the overall QoL would improve after the treatment, the self-rated SAQOL-39 was analysed by comparing the mean scores (Table 6). The participant's responses indicated that QoL based on the overall SAQOL-39 self-rated score improved between the baseline average ($M = 3.63$) and posttherapy ($M = 4.51$) by 18%, and it was maintained at follow-up ($M = 4.23$).

Table 5: Raw scores for personal stroke narrative analysis based on the SSLA.

| | Baseline 1 | Baseline 2 | Baseline 3 | Baseline avg | Post-therapy | Follow-up |
|---|---|---|---|---|---|---|
| Utterances | 12.00 | 14.00 | 7.00 | 11.00 | 12.00 | 18.00 |
| Rate | 99.37 | 152.41 | 98.50 | 116.76 | 141.60 | 152.22 |
| Length | 58% | 43% | 14% | 39% | 50% | 17% |
| Melody | 3.00 | 3.00 | 3.00 | 3.00 | 2.00 | 4.00 |
| Articulation | 7.00 | 7.00 | 7.00 | 7.00 | 7.00 | 7.00 |
| Complexity | 42% | 50.00% | 72% | 54% | 33% | 61% |
| Errors | 17% | 57% | 57% | 44% | 50% | 33% |
| C.U.s | 19.00 | 22.00 | 17.00 | 19.33 | 21.00 | 36.00 |
| Paraphasias | 0% | 0% | 0% | 0% | 0% | 0% |
| Repetitions | 0% | 21% | 0% | 7% | 0% | 22% |
| Communication efficiency | 12.03 | 15.17 | 12.78 | 13.33 | 16.80 | 17.73 |

Table 6: Quality of life for C.S. at pretreatment (baseline) at posttreatment and 3-month follow-up using the SAQOL-39g.

| Item (max score: 5) | Baseline 1 | Baseline 2 | Baseline 3 | Post-therapy | Follow-up |
|---|---|---|---|---|---|
| SAQOL-39 g mean | 3.44 | 3.41 | 4.05 | 4.51 | 4.23 |
| Physical | 4.31 | 3.88 | 4.56 | 4.75 | 4.88 |
| Communication | 3.57 | 3.71 | 4.14 | 4.43 | 4.14 |
| Psychosocial | 2.50 | 2.88 | 3.56 | 4.38 | 3.56 |

## 4. Discussion

The main objective was to explore the potential domains of transfer effects after stimulating the left DLPFC combined with WM training and also to measure how this affected the quality of life of the participant. In a previous pilot study [10], we found evidence signifying the possible improvement that could specifically yield from noninvasive brain stimulation programs using iTBS combined with the *RehaCom* WM training program in PWA. Studies performed on healthy aging which are usually focused on prevention, consider the use of rTMS as a tool for cognitive enhancement of the elderly with mild cognitive impairments (MCI), aimed at reversing or compensating for the cognitive deficits [55, 56]. Evidence suggests that the effects of rTMS application may work in synergy with cognitive training to give rise to greater neurocognitive enhancement [55, 57, 58], supporting the notion that cognitive rehabilitation with rTMS can be beneficial as an add-on instrument in cognitive training programs of a variety of neurological and cognitive disorders [59]. A recent review investigating the effects of rTMS in people with Alzheimer's disease and related dementias (ADRD) reported 8 new studies between the years 2016 and 2018, of which 4 of them used cognitive training as well [60]. These studies reported significant improvements in global cognition and memory when measured with the following neuropsychological tests: Alzheimer's Disease Assessment Scale-cognitive (ADAS-Cog), Mini Mental State Exam (MMSE), Addenbrooke Cognitive Examination (ACE), Apathy Evaluation Scale (AES-C), Blessed Dementia Scale (BDS), Clinical Global Impression (CGI), Clinical Global Impression of Change (CGIC), Digit Symbol Substitution Test (DSST), Montreal Cognitive Assessment (MOCA), Neuropsychiatric Inventory (NPI), Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test (TMT), and Zarit Burden Scale (ZBS). Even though results suggested a potential for improvement in cognitive measures after rTMS treatments, results were mixed as to whether rTMS was significantly more effective than sham. It is believed that the inconsistency of treatment protocols and outcome measures hinders the replication of promising studies, and therefore, evidences continue to be insufficient to support the adoption of a noninvasive brain stimulation protocol to improve cognitive impairments.

In line with previous studies, findings from this investigation (Table 7) lend support to the evidence that (i) WM interacts with language abilities and deficits in WM influence language performance [10, 61], (ii) applying iTBS to the LDLPFC results in improved WM performance [10, 62, 63], (iii) computerized WM training can have positive outcomes on WM tasks [64], and (iv) aphasia has a negative effect on QoL [65].

*4.1. Near-Transfer Effects of iTBS and WM Training.* WM has been proven to be a useful indicator of cognitive-linguistic competence [66], while WM impairments have a negative impact on cognition and communication [67, 68]. It is important to highlight the fact that WM interventions have a positive impact on WM capacity, as well as on related cognitive-linguistic abilities and on cognitive-communicative deficiencies due to aging or neurological disorders [25, 69]. Furthermore, studies have demonstrated transfer of WM training to other assessments of cognition, including measures of fluid intelligence [27]. This study has revealed a trend for improvement in both WM tasks and Gf transfer, with a statistical significance of Gf as measured with the RCPM after the

Table 7: Task performance after the treatment.

| Task | Treatment results |
|---|---|
| WM–number of correct responses | Improved and maintained |
| RCPM | Non-significant improvement and maintenance in subtest AB |
| BDAE auditory comprehension | No improvement |
| BDAE oral expression | Significant improvement and maintenance in the Boston naming test |
| BDAE reading | Nonsignificant improvement and maintenance in matching cases/scripts and word identification<br>Significant trend for improvement in the overall reading task |
| Narrative (MAIN) | Non-significant improvement and maintenance |
| Procedural discourse | No improvement |
| Communication efficiency (SSLA) | Improvement and maintenance |
| QoL | Improvement and maintenance |

10-day iTBS application to the left DLPFC followed by the 30-minute WM training. It was also hypothesised that stimulation of the DLPFC combined with WM training would result in positive "near-transfer" cognitive effects with subsequent improved scores on untreated cognitive areas (i.e., Gf). A statistically significant overall trend for improvement was found in *Subtest AB* of the *RCPM*, a nontrained measure that indicates Gf (nonverbal intelligence) improvement ($t(11) = 1.82$, $p = 0.048$), while the overall score resulted in positive nonsignificant treatment effects. These findings are consistent with research showing that significant improvements in Gf resulting from cognitive intervention combined with different transcranial electrical brain stimulation protocols [70]. Our findings support the notion that Gf can be improved with DLPFC stimulation [70] and WM training [10, 71–73]. Considering the fact that a combination of treatments was used and it is still controversial whether WM training leads to Gf improvement [74], the findings are inconclusive as to whether improvement was due to the treatment combination or to the DLPFC stimulation. It is worth investigating further whether this association is significant in future research.

*4.2. Far-Transfer Effects of iTBS and WM Training.* In the past, other groups of researchers focused on investigating improvements in *Auditory Comprehension* where they showed that WM training was used to improve receptive language abilities in PWA [75–79]. These aforementioned studies reported language improvements in tasks such as commands and naming when measured on language tests such as the Western Aphasia Battery (WAB), the Test for the Reception of Grammar (TROG), and the Token Test (TT). The participant of this study had been experiencing mild expressive aphasia with STM difficulties. Results of the treatment showed a significant overall trend for improvement in the *Boston Naming Test* of the *BDAE Oral Expression* subtest. These results tie in well with previous studies where noninvasive brain stimulation to the left prefrontal cortex generated verbal working memory improvements and naming facilitation [10, 80]. Additionally, there was a significant trend for improvement in the overall *BDAE Reading* subtest; although when the individual tasks were analysed, significance was not reached. These results are in agreement with our previous research in which reading abilities were improved [10]. To the best of our knowledge, no other studies so far have investigated language improvements following iTBS combined with WM training with regard to naming or reading.

Two types of tasks were used to collect narrative discourse: the Baby Goat story from the *MAIN* [38] and a personal stroke narrative [37]. The participant showed a nonsignificant trend for improvement in the narrative, specifically showing improvement in the IST initiating structure of the story. Evidence supports that WM impairment in PWA adversely affects their ability to produce macrolinguistic narrative components [81] and higher scores on WM measures are associated with better discourse production abilities in people with brain injury [82]. The SSLA system (Shewan, 1988) was used in this study to examine the broad spectrum of language variables, in order to analyse and quantify the personal stroke narrative. The participant showed a positive linear trend in the *Rate* of speech and *Sentence Complexity*, while there was a negative linear trend in *Errors* indicating improvement. Although linguistic analysis was not generally used in the aphasia treatment literature to evaluate changes in linguistic complexity, there is an increase in research on the topic over the last few years [83]. Even though language sample analysis is commonly used to evaluate linguistic development in children [84], verbal abilities have been examined by analysing language samples [85, 86]. Few studies in the aging literature involving language analysis by obtaining oral language samples through prompts or through conversation [87]. A positive trend towards improvement in discourse was noted for both language tasks, which are consistent with the results of our previous pilot study [10].

Procedural Discourse analysis was based on the analysis developed by Richardson and Dalton [39]. The participant did not show any changes in the responses across the five periods in the *Procedural Discourse* task. Although improvements in these tasks did not reach significance, findings are in agreement with research from the aphasia literature on discourse tasks [88–91]. From the aforementioned studies, only one study was specifically directed to procedural discourse [92], with the more recent studies [88, 89, 91] exploring all aspects of discourse production, including narratives, revealing that as aphasia severity increases, quality and

quantity of relevant discourse decrease. The reduction in sentence complexity experienced by PWA has also been shown to differ at a single word and semantic level, which is likely to affect procedural discourse, suggesting that PWA communicate less information in language in a context where spoken language may already be structurally less complex [93]. PWA use fewer correct information units (CIU; i.e., any single word, intelligible, informative, and relevant in context) in discourse than neurologically healthy people (NHP) [94], as well as fewer types and tokens of spatial language in spatial tasks than NHP [95].

The investigation of the use of iTBS in aphasia rehabilitation poststroke continues to be very limited. There are a few studies though that provide evidence for its efficacy. When iTBS was applied in eight individuals with chronic aphasia poststroke for five consecutive days over the course of two weeks, six patients showed significant pre-/post-rTMS improvements in semantic fluency in which the participants were able to generate more appropriate words when prompted with a semantic category. Additionally, increases in the left frontotemporoparietal language networks with a significant left hemispheric shift in the left frontal, left temporoparietal, and global language regions were reported at the pre-/post-rTMS fMRI maps of the study [96]. Further to iTBS investigations, Georgiou et al. [97] recently reported promising findings of neuronavigated continuous theta-burst stimulation (cTBS) over the right pars triangularis (Tr) as a standalone treatment for two individuals with chronic poststroke aphasia in which cTBS was carried over 10 consecutive days for 40 secs per sessions. Their results revealed improvement in language skills in the post-treatment phase, which reverted to baseline scores at follow-up and improvement in the QoL [97].

The self-reported SAQOL-39 questionnaire was administered to C.S. in an interview format to rate his current levels of QoL. A positive linear trend for improvement in the overall QoL across time was noted, which was also maintained 3 months after the treatment, with prominent improvements in the communication and psychosocial fields. This is in line with the QoL literature that the improvement in the severity of language deficits has a positive effect in the QoL [98]. Moreover, the results are consistent with what has been found in previous research that nonverbal cognitive impairments may significantly affect QoL in PWA and are potentially important predictors to improvement [99].

## 5. Conclusions

The relationship between treatment of WM deficits and the impact on language abilities in poststroke aphasia was investigated. The purpose was to determine whether WM is improved after applying excitatory noninvasive brain stimulation (iTBS) followed by computerized WM training. Furthermore, it was important to decipher whether WM improvements lead to near-transfer on unpractised WM tasks and nonverbal intelligence and far-transfer effects on language tasks, narratives, functional communication and QoL. Overall, we report improvement in memory, fluid intelligence, language, and QoL after 10 sessions of iTBS combined with computerized WM training in a single case study with no adverse effects during treatment and at follow-up periods. As it is widely acknowledged amongst rehabilitation professionals, the deficits acquired after a stroke persist for long periods and positive effects are accomplished at a slower rate. The results of this study are indicative that computerized WM training and stimulation of the LDLPFC are areas that have a positive effect in neurorehabilitation of PWA after a stroke. Improvements were noted in only 10 days and even though not all the benefits were maintained at follow-up (3 months post), the positive linear trendlines signify that there is efficacious treatment potential, which requires further exploration towards facilitating language recovery in PWA. It is important to consider that aphasia treatment programs could benefit from neurorehabilitation to increase the pace of recovery, especially during the first months of rehabilitation. The results of this study provide a preliminary indication that stimulation of the LDLPFC combined with computerized WM training after left hemisphere stroke may generalize to language improvements.

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

## Acknowledgments

The authors would like to acknowledge the Cyprus Stroke Association and the Melathron Agoniston EOKA, Limassol, Cyprus for their assistance with participant recruitment.

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Hindawi
Behavioural Neurology
Volume 2021, Article ID 9417173, 10 pages
https://doi.org/10.1155/2021/9417173

*Research Article*

# Associations between Upper Extremity Motor Function and Aphasia after Stroke: A Multicenter Cross-Sectional Study

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Received 9 July 2021; Revised 8 October 2021; Accepted 18 October 2021; Published 9 November 2021

Academic Editor: Grigorios Nasios



*Background and Purpose*. Poststroke aphasia (PSA) often coexists with upper extremity (UE) motor dysfunction. However, whether the presence of PSA affects UE motor performance, and if language function associates with UE motor performance, are unclear. This study is aimed at (1) comparing the motor status of UE between patients with PSA and without PSA and (2) investigating the association between language function and UE motor status in patients with PSA. *Methods*. Patients with stroke were compared and correlated from overall and three periods (1-3 months, 4-6 months, and >6 months). Fugl-Meyer assessment for the upper extremity (FMA-UE) and action research and arm test (ARAT) were used to compare the UE motor status between patients with PSA and without PSA through a cross-sectional study among 435 patients. Then, the correlations between the evaluation scale scores of UE motor status and language function of patients with PSA were analyzed in various dimensions, and the language subfunction most closely related to UE motor function was analyzed by multiple linear regression analysis. *Results*. We found that the scores of FMA-UE and ARAT in patients with PSA were 14 points ((CI) 10 to 18, $p < 0.001$) and 11 points lower ((CI) 8 to 13, $p < 0.001$), respectively, than those without PSA. Their FMA-UE ($r = 0.70$, $p < 0.001$) and ARAT ($r = 0.62$, $p < 0.001$) scores were positively correlated with language function. Regression analysis demonstrated that spontaneous speech ability may account for UE motor function ($R^2 = 0.51$, $p < 0.001$; $R^2 = 0.42$, $p < 0.001$). Consistent results were also obtained from the analyses within the three time subgroups. *Conclusion*. Stroke patients with PSA have worse UE motor performance. UE motor status and language function showed positive correlations, in which spontaneous speech ability significantly accounts for the associations.

## 1. Introduction

Patients after stroke who have both upper extremity (UE) motor impairment and/or language dysfunction are common [1]. These two types of poststroke dysfunction are the most apparent neuropsychological deficits occurring after stroke: UE motor deficit occurs in about 80% of stroke survivors, aphasia in 21%-38%, and cooccurrence in about 24% [2–4]. PSA with UE motor dysfunction impacts social participation and quality of life, and it can also be associated with multiple comorbidities and lead to worse prognosis [5, 6]. Due to the adjacent anatomical location, ischemia or hemorrhage in the middle cerebral artery (MCA) often leads to UE motor dysfunction and nonfluent aphasia. Nevertheless, there are small samples of study that have analyzed the relationship between hand-arm motor dysfunction and aphasia using lesion volume and location as control variables, showing that the association is not determined by anatomical relationships alone. The extents and limitations of UE and language cortical reciprocity remain under debate; it is likely that UE movement and language have shared neural correlates not merely depending on anatomical proximity and vascular factors.

In Huashan Hospital, there is an original operation, a contralateral seventh cervical nerve transfer to improve UE motor function in patients with chronic central injury [7]. After the surgery, we found that patients with PSA not only improved their UE motor status but also their language function. These phenomena suggest a deep neural mechanism relationship between language function and UE motor status after stroke. Several studies [8–11] have focused on the potential relationship between UE motor status and language function. From a human evolution perspective, language was spurred by freedom of hand movement as an additional consequence of this upright posture. Gestures are a combination of UE movements and language [12]. A retrospective cohort study addressed the possible interaction between motor impairment and aphasia recovery after stroke. Motor responders showed better linguistic performances at the final aphasia assessment than motor nonresponders, while language responders reached a higher level of motor functioning than language nonresponders [8]. Meanwhile, a significant response in one domain was not associated with any deterioration in the other. Furthermore, Harnish et al. examined five patients with aphasia and hemiparesis poststroke during six weeks of UE therapy but not receiving speech therapy. Patients were assessed not only for the UE motor recovery but also for changes in their language abilities. fMRI data demonstrated shifts in increased blood oxygen improvements in both UE motor status and language function scores [13]. However, current studies rarely focus on simultaneous UE motor dysfunction with language deficits and even less on both functions' concurrent recovery during stroke recovery. Most studies only unexpectedly found this phenomenon or were mostly exploratory paradigm intervention studies [1, 14–16]. Few studies have focused on the difference in UE motor function status between patients with PSA and nonphasic poststroke patients. Moreover, no study provides evidence on the correlation between UE motor status and language function after stroke [8, 9], which leads to low attention to UE-language correlation so that UE and speech-language therapies are completely separated during UE motor and (or) speech rehabilitation.

To cover this gap, the present study investigated the UE motor status and language function of stroke patients by a cross-sectional investigation. We hypothesized that there were differences in motor status between stroke patients with PSA and without PSA and that there were some relationships between the speech-language function and UE motor status in patients with PSA.

Therefore, the objectives of this study were (1) to compare the UE motor status between patients with PSA and without PSA, (2) to investigate the association between language function and UE motor status in patients with PSA, and (3) based on (2), to determine which dimension of PSA evaluation is most closely related to the UE motor status.

## 2. Methods

*2.1. Study Population and Design.* This study was conducted between May 2020 and June 2021 in the departments of rehabilitation medicine of six hospitals from different regions in China. Patients were consecutively screened for the following criteria: (1) aged 18 years or older; (2) native Chinese speaker, (3) stroke onset > 1 week, (4) with a primary diagnosis of acute cerebrovascular accident according to the WHO diagnostic criteria confirmed by computed tomography (CT) or magnetic resonance imaging (MRI), (5) underwent rehabilitation assessed by a team of specialists (physicians, speech therapists, and occupational therapists), and (6) had ability to complete all the assessment. However, individuals were excluded if the consent of the patient's family could not be obtained; if there was no imaging available; if they had a previous history of stroke; if they had a severe hearing impairment or visual impairment; if they had other primary medical conditions that could influence language and motor function; such as a brain tumor, Parkinson's disease, severe poststroke depression, and Alzheimer's disease; or if they had undergone surgical evacuation.

Patients were evaluated in a single test session performed by speech therapists and occupational therapists who had received consistency training. One trained researcher performed the data collection. Patients' baseline characteristics were evaluated, including age at stroke onset, gender, comorbidities, hand dominance, time poststroke, lateralization, and stroke type. After 2326 patients were screened, those who met the above conditions participated in this study, 214 among whom with PSA were in the observational PSA group. A group of 221 patients without PSA after stroke matched for age and sex participated and were distributed into the non-PSA group as controls. The sample sizes were estimated referring to other similar studies [8, 17, 18]. As an important outcome, the UE motor impairment and function between the two groups were compared. Further evaluation was done in the observational PSA group to see the association between UE motor status and language function

evaluation scores. For further validation purposes, the relationships between them were analyzed by multiple linear regression. Then, to observe the difference between different time periods from stroke onset, subsequent stratification analyses by time (1-3 months, 4-6 months, and >6 months) were performed. Our study used a cross-sectional observational design. The ethics committee approved the study protocol of Huashan Hospital of Fudan University and all participating centers according to the 1964 Declaration of Helsinki's ethical standards and its later amendments. This trial is registered with ChiCTR2000033792. All patients or their families provided written informed consent before study enrollment.

*2.2. Measurement Instruments and Evaluation*

*2.2.1. Evaluation of PSA: Aphasia Quotient of Western Aphasia Battery-Revised (WAB-AQ) and Boston Diagnostic Aphasia Examination (BDAE).* PSA was evaluated using the Chinese version of WAB-AQ, a commonly used clinical evaluation of PSA that assesses the presence, type, and severity of aphasia with a 0-100 scale (score < 93.8 are indicative of aphasia). The WAB-AQ elaborately evaluates the domains of expression and comprehension, yielding summary scores for the following four domains: spontaneous speech, auditory verbal comprehension, repetition, and naming. The four dimensions of scores were recorded and counted. AQ, the weighted composite of these four scores, was used as the independent variable of interest in this study and is indicative of the overall severity of the patients' PSA. On the other hand, for easy screening and observation, the BDAE severity grading standard was chosen to classify the severity of patient language dysfunction with grade criteria of 0, 1, 2, 3, 4, and 5 [19]. Grade 0 is meaningless language or auditory comprehension, while grade 5 is a barely recognizable language disorder, and the patient may have some subjective difficulties, but it is not easy for the listener to detect. All patients have to be assessed by BDAE, and only if the grade < 5 will WAB-AQ be evaluated.

*2.2.2. Evaluation of UE Motor Impairment: Fugl-Meyer Assessment for the Upper Extremity (FMA-UE).* The FMA was used to assess extremity motricity, balance, some sensory details, and joint dysfunction in hemiplegic patients. We evaluated the only motor function of the UE, including measurement of voluntary movement, velocity, coordination, and reflex activity. A total of 33 items are included. A 3-step (0-1-2) ordinal scale is applied to each item (0 = details cannot be performed; 1 = details are performed only partly; 2 = details are performed throughout the full range of motion of the joint). This gives a total maximum score of 66, which defines a normal motor function (42 and 14 for the arm and hand, respectively). FMA-UE mainly aims at evaluating UE motor impairment and dysfunction after stroke.

*2.2.3. Evaluation of UE Motor Function: Action Research Arm Test (ARAT).* Instruments needed to perform the test are as follows: woodblocks, a ball, a washer and bolt, a stone, two different sizes of alloy tubes, two glasses, a marble, and a 6 mm ball bearing (instrument model: OT-KL-40400). The test is a 4-grade scale ranging from 0 to 3 with a maximum score = 57 (0 = can perform no part of the test; 1 = can perform the test partially; 2 = can complete the test but takes an abnormally long time or has great difficulty; and 3 = can perform test normally). ARAT is a quantitative test for the UE function and includes four subsets: grasp, grip, pinch, and gross movement. Both ARAT and FMA-UE are widely used and are the most recognized methods to evaluate the motor status of UE in patients with stroke. The difference is that ARAT is mainly aimed at motor function assessment and activity measurement, while FMA-UE pays more attention to dysfunction and impairment.

*2.3. Statistical Analysis.* Data were analyzed with IBM SPSS Statistics version 26.0. Demographics and clinical variables, presented as mean ± standard deviation for continuous variables and proportions for categorical variables, were compared between observation and control groups using the independent sample Student $t$-test, the Chi test, and the Mann–Whitney $U$-test, as appropriate. The Spearman correlation analysis between WAB-AQ and FMA-UE scores was made to address the association question. Then, to eliminate the influence of some factors on the correlation analysis, the correlation coefficients between WAB-AQ and FMA-UE are corrected for age, education, and duration post-stroke. Similarly, this method is also used between WAB-AQ and ARAT scores and between the four parts of WAB-AQ (spontaneous speech, understanding, repetition, and naming) and FMA-UE as well as ARAT scores. In addition, all patients were stratified according to 3 time periods (1-3 months, 4-6 months, and >6 months) and compared, and correlated analyses were performed within each of the three periods by the same method as the overall analysis. In the end, we performed two multiple linear regression analyses, using the "enter" method, to determine which dimension of WAB-AQ was the most informative in accounting for the UE motor function with WAB-AQ including spontaneous speech, comprehension, repetition, and naming scores as independent variables and ARAT or FMA-UE scores as dependent variables.

## 3. Results

*3.1. Demographics.* From a total of 2326 patients, we excluded 1891, leaving 435 patients for analysis (see Figure 1). 435 patients underwent a complete systematic assessment with a median course of 15 weeks (IQR: 7-32). The median age of the patients was 60.6 years (SD = 11.2). A total of 153 were female, and 282 were male. Table 1(a) shows the patient characteristics, presented for the total group and for the patients with PSA ($n = 214$, 49.2%) and without PSA ($n = 221$, 50.8%). 370 patients suffered from ischemic stroke and 65 from hemorrhage. A total of 330 patients showed right-sided hemiparesis, while 105 patients showed left-sided hemiparesis. Stratification according to stroke duration showed 69 in the PSA group and 76 in the non-PSA group for patients stratified according to a period of 1-3 months; 69 in the PSA group and 72 in the non-

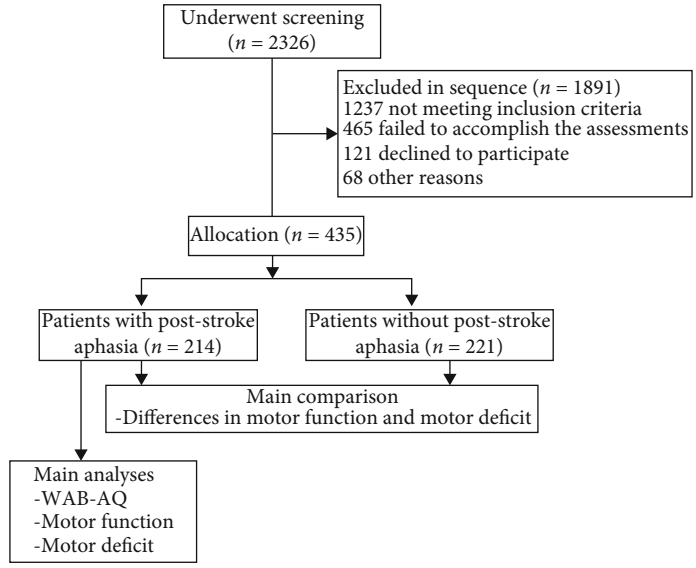


Figure 1: Flow chart of the study sample and procedures of the comparison and analyses. WAB-AQ indicates the Western Aphasia Battery-Aphasia Quotient; FMA-UE indicates the Fugl-Meyer assessment for the upper extremity; ARAT indicates the action research and action test.

PSA group for patients stratified according to a period of 4-6 months; and 76 in the PSA group and 73 in the non-PSA group for patients stratified according to a period >6 months. No statistically significant difference was found in age, gender, comorbidities, hand dominance, time post-stroke, and type of stroke between groups.

*3.2. Comparison between Groups and Distribution of PSA Group.* The FMA-UE and ARAT scores were compared between groups through the Wilcoxon rank sum test. The confidence interval estimation of median difference based on the Wilcoxon rank sum test is obtained by the Hodges-Lehmann method. The contrast revealed a significant difference between groups ($p < 0.001$; Table 1(b)), and it showed that the non-PSA group had significantly higher scores than the PSA group ($p < 0.001$, Figure 2). Detailed scores of the four dimensions in the 214 PSA patients are summarized in Table 1(b). After stratification according to the stroke time, the three comparisons (PSA versus non-PSA) of subgroups (1-3 months, 4-6 months, and >6 months) still obtained consistent results ($p < 0.001$, Figure 2).

*3.3. Correlations between PSA and Motor Function and Deficit.* Table 2 illustrates the results of the correlation analyses between language functions (WAB-AQ, spontaneous speech, comprehension, repetition, and naming score) and UE motor status (FMA-UE and ARAT scores) from the overall perspective and from the perspective of the three time periods. We adjusted the correlation coefficients with age, education, and duration poststroke. Overall, moderate to strong positive correlations were found between WAB-AQ and ARAT score ($r = 0.62$, $p < 0.001$, Figure 3(b)). Further, there were stronger correlations between WAB-AQ and FMA-UE score ($r = 0.70$, $p < 0.001$, Figure 3(a)). For all the factors analyzed, their correlation coefficients varied from 0.45 to 0.72, of which the weakest correlation was comprehension, and the strongest was spontaneous speech. All results of partial correlation analysis, taking age, education, and duration poststroke as covariates, are shown in Table 2. Consistent with overall correlation results, the results of the partial correlation analyses according to the time stratification are shown in Table 2. We found that the highest correlation coefficient was WAB-AQ and FMA-UE in 4-6 months ($r = 0.76$, $p < 0.001$). Overall, the time stratification association trends were consistent with the overall analyses (see Figure 4).

*3.4. Factors Associated with Motor Dysfunction.* Two multiple linear regression analyses were performed to identify the most related factors that affect ARAT and FMA-UE scores. In the first regression model between four variables of WAB-AQ (spontaneous speech, comprehension, repetition, and naming score) and ARAT score, the results demonstrated that the four independent variables of WAB-AQ explained 42% of the variance in the ARAT score ($R^2 = 0.42$, $p < 0.001$). However, only the spontaneous speech score was significant ($R^2 = 0.42$, $p < 0.001$, Figure 3(d)). The other three variables had no significant difference ($p > 0.05$). The second regression model also examined the four independent variables with the FMA-UE score. The results demonstrated that the four independent variables of WAB-AQ explained 51% of the variance in the FMA-UE score ($R^2 = 0.51$, $p < 0.001$). Similarly, only the spontaneous speech score was significant ($R^2 = 0.51$, $p < 0.001$, Figure 3(c)); the other three variables had no significant difference ($p > 0.05$).

## 4. Discussion

Our results demonstrated that the UE motor status of patients without PSA is better than those with PSA, and there are positive relationships between UE motor status and language functions in patients with PSA (see Table 2). Spontaneous speech ability, one of the language functions, is most closely related to UE motor status, which explained

Table 1

(a) Comparisons of demographic data between the PSA group and the non-PSA group

| | PSA group ($n = 214$) | Non-PSA group ($n = 221$) | $p$ value |
|---|---|---|---|
| Female, $n$ (%) | 82 (38.3) | 71 (32.1) | 0.176[b] |
| Age, mean (SD) (y) | 61.1 ± 11.9 | 60.1 ± 10.4 | 0.340[a] |
| Education, mean (SD) (y) | 10.32 ± 3.7 | 10.91 ± 5.4 | 0.184[a] |
| Duration poststroke, median (IQR) (week) | 16 (6-35) | 14 (7-32) | 0.316[c] |
| Type of injury, $n$ (%) | | | 0.586[b] |
| Ischemia | 180 (84.1) | 190 (86.0) | |
| Hemorrhage | 34 (15.9) | 31 (14.0) | |
| Affected limb, $n$ (%) | | | 0.297[b] |
| Right | 167 (78.0) | 163 (73.8) | |
| Left | 47 (22.0) | 58 (26.2) | |

(b) Comparisons of clinical variables between the PSA group and the non-PSA group

| | PSA group ($n = 214$) | Non-PSA group ($n = 221$) | Mean difference (95% CI) | $p$ value |
|---|---|---|---|---|
| Motor evaluation, median (IQR) | | | | |
| FMA-UE | 20 (7-40) | 35 (23-52) | 14 (10, 18) | <0.001[c] |
| ARAT | 5.5 (0-30) | 21 (11-45) | 11 (8, 13) | <0.001[c] |
| Language evaluation, median (IQR) | | | | |
| BDAE | 1.57 ± 1.18 | 5 | -3.43 (-3.6, -3.3) | <0.001[d] |
| WAB-AQ | 44.6 (18.1-70.6) | | | |
| Spontaneous speech | 7.0 (2.0-13.0) | | | |
| Comprehension | 126.0 (60.0-175.0) | | | |
| Repetition | 50.0 (9.8-80.0) | | | |
| Naming | 27.0 (0.8-67.3) | | | |

[a]Two independent sample $t$-test. [b]$\chi^2$ test. [c]Wilcoxon's rank sum test. [d]Single sample $t$-test. Abbreviations: SD indicates standard error of the mean; IQR indicates interquartile range; CI indicates confidence interval; FMA-UE indicates the Fugl-Meyer assessment of the upper extremity; ARAT indicates the action research and action test; BDAE indicates the Boston Diagnostic Aphasia Examination; WAB-AQ indicates the Western Aphasia Battery-Aphasia Quotient.

51% of the variance in the motor deficit and 42% in motor function, respectively (see Figures 3(c) and 3(d)). Previous studies have mentioned that the recovery of motor and language function is operated in parallel [20–23]. Due to the lack of data demonstrating UE motor status associated with language function, current stroke rehabilitation evaluations and therapies have treated these two symptoms separately [8, 24]. Patients with PSA receiving speech-language therapy are frequently seated during treatment, with UE impassive and motionless [9]. Our results supported the hypothesis that poststroke patients' UE motor status and language function are highly correlated, and UE motor status assessment and therapy should be integrated into the treatment for patients with PSA [9].

Similar to the findings of previous studies [25, 26], after evaluation of FMA-UE, ARAT, and WAB-AQ, we found that the evaluation scores of patients with PSA were significantly lower than those of nonaphasia patients with no difference in age, educational background, and course of stroke between the two groups not only from an overall perspective but also from three time perspectives (see Figure 4). PSA is independently associated with increased complications and length of stay during the acute stroke admission after controlling for NIHSS score, with an effect comparable to severe hemiparesis, and sometimes greater [26]. Likewise, patients with PSA have lower motor Functional Independence Measures (FIM) and cognitive FIM scores both at admission and at discharge, compared to those without PSA during the subacute and chronic period [25]. Our findings support their findings and provide a supplement and explanation for this phenomenon. FIM is a routine assessment in stroke rehabilitation centers to quantify the ability to perform daily activities after stroke with a 7-point scale for 5 cognitive and 13 motor tasks such as getting dressed, bowel, and grooming control [10]. FMA-UE and ARAT scales are specifically used to evaluate UE motor deficit and motor function for stroke patients [20]. Overall, our results provide preliminary evidence why aphasia patients have worse FIM scores and long hospitalization.

Hybbinette et al. [27] confirmed the common occurrence of apraxia of speech and aphasia in left hemisphere stroke patients with a hand motor impairment through a

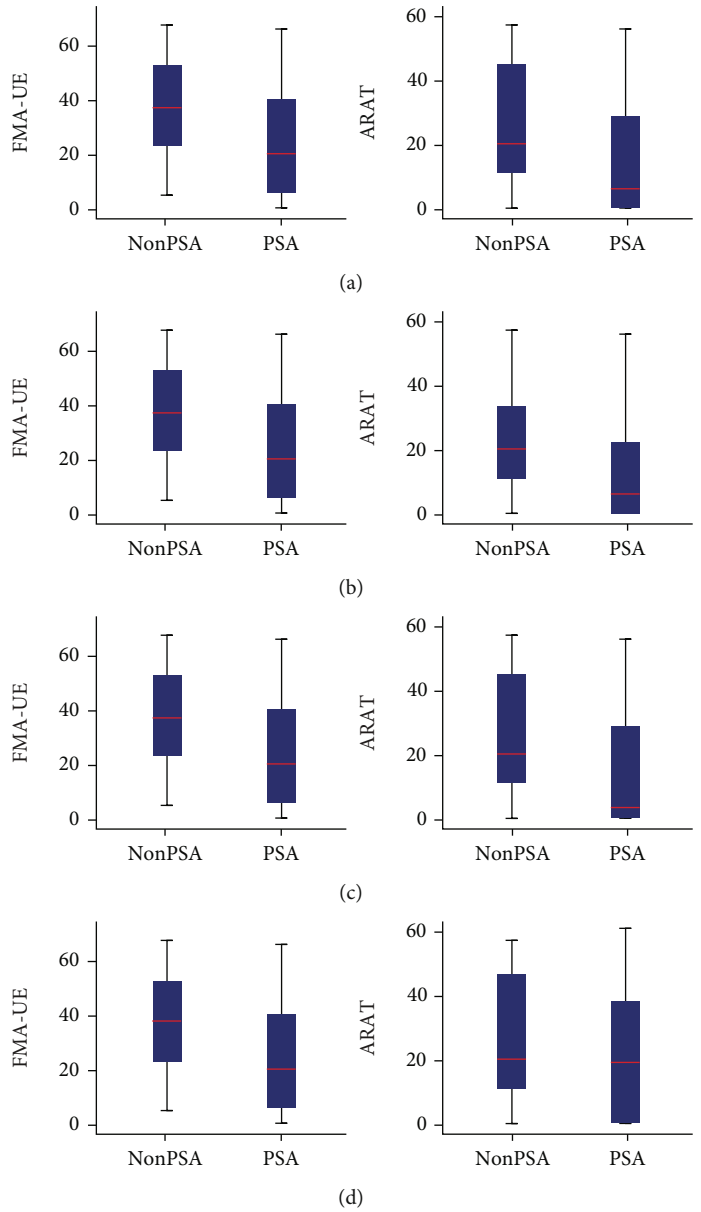


Figure 2: Clinical measurement of the FMA-UE and ARAT scores. (a) Comparison of the FMA-UE and ARAT total scores between the non-PSA and PSA groups. (b–d) Comparisons of the FMA-UE and ARAT total scores between the non-PSA and PSA groups in 1-3 months, 4-6 months, and >6 months. Significant differences were observed in both groups. $p < 0.001$. Abbreviation: non-PSA indicates patients without poststroke aphasia; PSA indicates patients with poststroke aphasia; FMA-UE indicates the Fugl-Meyer assessment for the upper extremity; ARAT indicates the action research and action test.

small sample study. Our correlation analyses results show that the four dimensions of language function—spontaneous speech, comprehension, repetition, and naming—were all associated with UE motor status (see Figure 5). The correlation between spontaneous speech and UE motor status is the strongest, while the correlation of comprehension is the weakest among the four dimensions. Because some patients have been paralyzed for a long time, the ARAT scale has basic requirements for the UE function. Some of the patients had low or even zero scores of ARAT, which reduce the correlation coefficient to a great extent (seeing Figure 3(b)). Furthermore, regression analyses show that spontaneous speech ability can account for UE motor status to some degree. Consistent with previous studies, our results make their conclusions more convincing that the Aachen aphasia test (AAT) is a predictor of functional outcome in patients with aphasia [26]. Its predictive power is like that of other functional tests commonly recognized to predict outcome strongly. Among the language functions in AAT, comprehension seems to be the most important predictive factor of the total and cognitive FIM, while spontaneous speech ability seems to be a motor-FIM predictor. There were unexpected findings in previous studies that in the treatment of UE motor deficits, the patient's language function was

Table 2: Pearson's correlation between four parts of WAB-AQ and FMA-UE and ARAT scores.

| Language motor | WAB-AQ | $r$ Spontaneous speech | Comprehension | Repetition | Naming |
|---|---|---|---|---|---|
| FMA-UE† | 0.70 | 0.72 | 0.53 | 0.60 | 0.64 |
| ARAT† | 0.62 | 0.66 | 0.45 | 0.52 | 0.57 |
| FMA-UE* | 0.59 | 0.60 | 0.46 | 0.52 | 0.46 |
| ARAT* | 0.54 | 0.60 | 0.42 | 0.42 | 0.45 |
| FMA-UE** | 0.76 | 0.76 | 0.57 | 0.65 | 0.72 |
| ARAT** | 0.68 | 0.68 | 0.48 | 0.57 | 0.67 |
| FMA-UE*** | 0.71 | 0.76 | 0.52 | 0.62 | 0.67 |
| ARAT*** | 0.65 | 0.70 | 0.46 | 0.58 | 0.61 |

†Correlation analyses of the overall time period. *Correlation analyses of 1-3 months. **Correlation analyses of 4-6 months. ***Correlation analyses of >6 months. FMA-UE indicates the Fugl-Meyer assessment for the upper extremity; ARAT indicates the action research and action test; WAB-AQ indicates the Western Aphasia Battery-Aphasia Quotient. $p < 0.001$. The correlation coefficients are corrected for age, education, and duration poststroke.

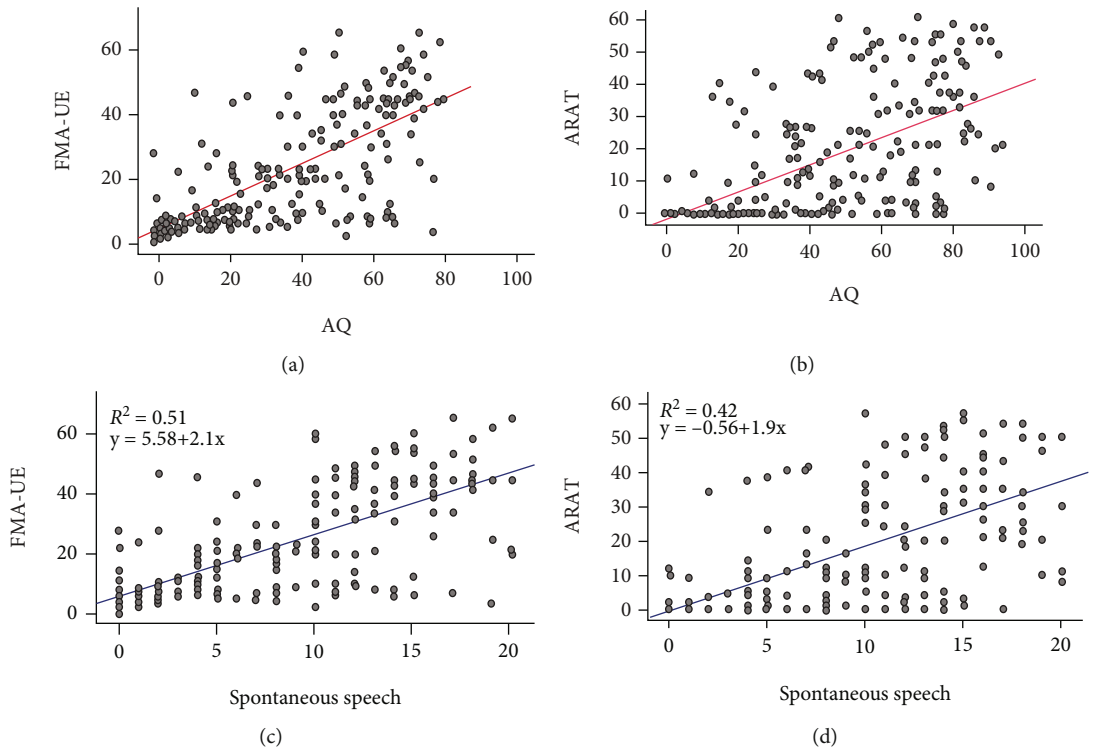


Figure 3: Correlation and regression in independent evaluation scores. (a, b) The association of AQ with FMA-UE and ARAT is shown. (c, d) The correlation of spontaneous speech and FMA-UE and ARAT is shown using linear regression equation. $p < 0.001$. FMA-UE indicates the Fugl-Meyer Assessment of the Upper Extremity; ARAT indicates the action research and action test; AQ indicates the Western Aphasia Battery-Aphasia Quotient.

improved, or when the PSA was treated, the UE motor function was improved [15, 28–31]. For example, transcranial direct current stimulation (tDCS) is utilized to stimulate the left primary motor cortex (M1) to study its effect on language function. To explore its clinical effect, some researchers used M1-tDCS to intervene in patients with PSA. The results show that M1-tDCS can improve aphasia patients' motor and communication function in conjunction with enhancing the retrieval ability of action-related words in the long term [16]. Interestingly, studies demonstrated that language function could be improved by asking patients to watch videos of task-oriented movements of the UE with voice guidance [31]. Similarly, compared with the control group, some movements such as grip without phonetic guidance can also enhance patients' language function with PSA. However, the extent and limitations of UE and speech-language cortical reciprocity remain unclear, and whether the affected anterior brain regions of the language-dominant hemisphere are interwoven with proximate cortical areas supporting UE motor status [24].

Our results provide compelling evidence for the relation between UE motor status and language function in terms of

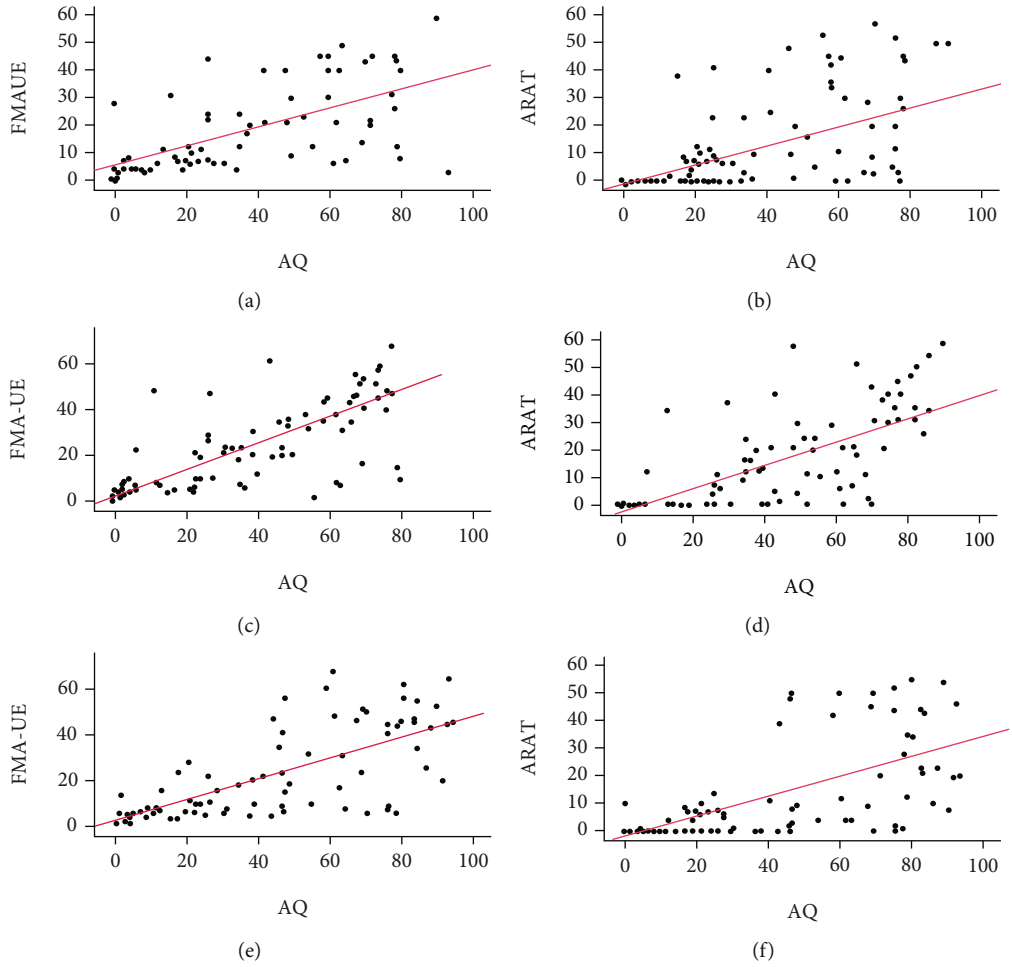


Figure 4: Correlations of independent evaluation scores in different times from stroke onset. (a, b) The association of AQ with FMA-UE and ARAT in 1-3 months is shown. (c, d) The association of AQ with FMA-UE and ARAT in 4-6 months is shown. (e, f) The correlation of AQ with FMA-UE and ARAT in >6 months. $p < 0.001$. FMA-UE indicates the Fugl-Meyer assessment of the upper extremity; ARAT indicates the action research and action test; AQ indicates the Western Aphasia Battery-Aphasia Quotient.

behavioral performances and demonstrate that this relationship can be applied to patients' therapy with PSA or UE motor deficit or both after stroke. Patients with PSA have worse hand and UE motor status, which calls for more attention to be given to UE motor rehabilitation in these patients. Interactions between the auditory system and the motor system are related to speech perception. The motor theory of perception has two basic claims: perceiving speech is perceiving gestures and perceiving speech involves the motor system. The mirror neuron system (MNS) is a multimodal system composed of neuronal populations that respond to motor, visual, and auditory stimulation, such as when an action is performed, observed, heard, or read about. In humans, the MNS has been identified using neuroimaging techniques. It reflected the integration of motor-auditory-visual information processing related to aspects of language learning, including action understanding and recognition [32]. Based on MNS, embodied cognition theory believes that various cognitive processes (such as concepts, categories, language, reasoning, and judgment) are closely related to the body's sensorimotor system [33, 34]. Therefore, the realization of language processing should take advantage of the brain motor network, that is, the interweaving and coupling of language processing and motor execution [35]. These theories can demonstrate our findings from the aspect of neural mechanisms.

Our study has some limitations. We did not classify patients according to recovery stage, severity, and the specific brain damage area in patients. Moreover, our study was performed in the cross-section without longitudinal follow-up; thus, whether the recovery stage affects their correlations is unclear. Furthermore, given the proximity of hand-arm and speech-language neural structures, in many patients with post-stroke aphasia, the contralesional UE is often simultaneously impaired so that the association between them seems inevitable [9]. However, we know that the Broca area (BA44,45) is adjacent to the UE motor cortex, which is mainly responsible for spontaneous speech ability. Nevertheless, in addition to spontaneous speech, naming, repetition, and comprehension are also positively associated with UE motor conditions, and there should be a deeper neural mechanism worth exploring. Another limitation is that although our study has a large

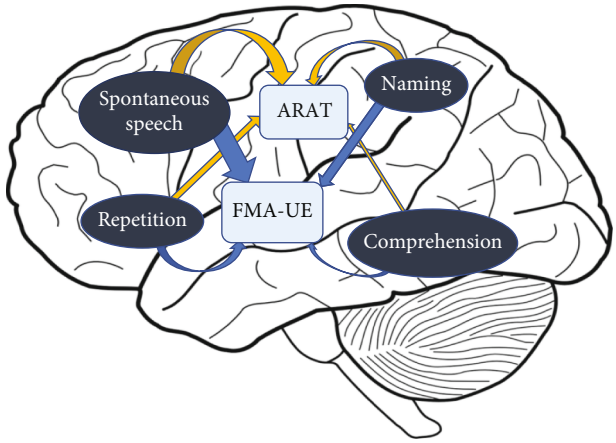


Figure 5: The association between UE motor status and language function after PSA. Schematic diagram shows partial correlations in an eight-way analysis of FMA-UE; ARAT; and spontaneous speech, comprehension, repetition, and naming. The degree of the arrow thickness between two modules is proportional to the correlation coefficient. FMA-UE indicates the Fugl-Meyer assessment for the upper extremity; ARAT indicates the action research and action test.

sample size, this also led to a less strict implementation of our inclusion and exclusion criteria, where some of the patients may have been accompanied by other symptoms after stroke. In addition, the fact that the patients were not specifically restricted in terms of damaged brain location and only excluded some patients with large brain lesion only, also diminished the persuasiveness of our findings, and we will go on to restrict these factors in our next study and try to get more rigorous conclusions.

## 5. Conclusion

To our knowledge, this is the first cross-sectional study to explore the relationship between UE motor status and language function after stroke. Our study demonstrated that patients with PSA tend to be with poorer UE motor status compared to those without PSA, and UE motor status is positively correlated with language function, especially for spontaneous speech ability. Future study should focus more on the deeper mechanisms of the link between UE motor status and language function after strictly controlling the location and severity of brain lesion. In addition, this study provides a new perspective and statistical evidence for a "combined assessment and therapy" approach to UE motor and speech-language rehabilitation, which remains to be demonstrated in future studies.

## Abbreviations

UE: Upper extremity
PSA: Poststroke aphasia
FMA-UE: Fugl-Meyer assessment for the upper extremity
ARAT: Action research and action test
WAB-AQ: Western Aphasia Battery-Aphasia Quotient
BDAE: Boston Diagnostic Aphasia Examination.

## Data Availability

Data are available from the corresponding author on reasonable request.

## Conflicts of Interest

The authors declare no financial or other conflicts of interest.

## Authors' Contributions

Shuo Xu and Zhijie Yan contributed equally to this work and are first authors.

## Acknowledgments

We would like to thank Dr. Wang Jianhui, Dr. Zhang Yanan, Dr. Wang Jinyu, Dr. Ge Junsheng, and Dr. Yang Yanhui, for their indispensable supports in the implementation of screening and evaluation of patients. This study was supported by the National Key Research & Development Program of the Ministry of Science and Technology of the People's Republic of China (Grant numbers 2018YFC2002300 and 2018YFC2002301), the National Science Foundation of China (Grant number 91948302), and the Foundation for Innovative Research Groups of National Natural Science Foundation of China (Grant number 82021002).

## Supplementary Materials

Details of functional assessment scales can be found in the supplemental file. *(Supplementary Materials)*

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Hindawi
Behavioural Neurology
Volume 2021, Article ID 6299462, 6 pages
https://doi.org/10.1155/2021/6299462

*Research Article*

# Oral Motor Treatment Efficacy: Feeding and Swallowing Skills in Children with Cerebral Palsy

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Received 17 July 2021; Accepted 24 September 2021; Published 25 October 2021

Academic Editor: Grigorios Nasios



This study is aimed at identifying the relationship between oral motor treatment and the improvement of abilities for feeding and swallowing in boys and girls with CP residing in the state of Yucatán. The sample consisted of 30 patients with a diagnosis of CP and the presence of ADT, with gross motor function levels from II to V, between 3 and 14 years old, of which 50% received oral motor treatment. The predominant diagnosis was spastic CP and tetraplegia. An interview was carried out with the tutor, the application of the gross motor skills scale, and an assessment of feeding skills. The feeding and swallowing skills that improved significantly with the oral motor treatment were mandibular mobility, tongue activity, abnormal reflexes, control of breathing, and general oral motor skills ($p \leq 0.05$). Within the sample that did not receive oral motor treatment, 46% presented low or very low weight and 40% referred recurrent respiratory diseases. In the end, it was concluded that feeding skills improve significantly with oral motor treatment, regardless of the severity of gross motor involvement. Likewise, oral motor treatment was associated with a lower presence of respiratory diseases and nutritional compromise.

## 1. Introduction

Cerebral palsy (CP) is the most common cause of severe physical disability and motor function deterioration in children. Its prevalence has been increasing as more children survive the neonatal stage and the worldwide incidence is estimated at 2 per 1000 births [1–3]. Motor disorders originated by CP are often accompanied by sensory, perception, cognition, communication, and behavior disorders, which are usually aggravated by other diseases such as epilepsy or malnutrition. Feeding and swallowing disorders (FSD) are the most common in children with CP. Swallowing is a complex sensory-motor process that coordinates the bilateral contraction/relaxation in the muscles of the mouth, tongue, larynx, pharynx, and esophagus, traditionally subdivided into four phases: preoral, oral, pharyngeal, and esophageal [4]. Dysfunction of the pharyngeal phase is very dangerous due to the increased risk or incidence of food aspiration in the airways leading to recurrent lung infections and, in severe cases, death by bronchoaspiration. The clinical effect of preoral and oral phases disorders are often chronic, such as malnutrition or recurrent infections, which is very common in children with CP [5–7].

Oral motor rehabilitation therapy in children with CP aims at reducing or eliminating swallowing disorders and promoting functional feeding [8]. Some studies suggest that intervention with oral motor therapy (OMT) has a beneficial effect on functional independence levels and improves the quality of life [9, 10] of patients with FSD; for example, after 8 weeks of OMT, it has been proved that the body mass

index increases while the use of feeding tubes reduces [11–13]. This proves the importance of OMT in patients with FSD. In this study, the purpose was to compare the feeding and swallowing skills in Yucatecan children that had received OMT with those who had not.

## 2. Materials and Methods

*2.1. Subjects.* Thirty children with CP diagnosis were included, with ages between three and fourteen years old ($8 \pm 4.07$), fourteen males (47%) and sixteen females (53%), which had been registered in physical rehabilitation centers in the city of Merida, Yucatan. All participants presented some FSD, according to the Eating and Drinking Ability Classification System (EDACS) [14], and attended physiotherapy sessions at the different centers they belonged to for at least one year before this study was conducted; some of them participated in OMT in the past and some other did not. All participants received oral feeding only.

*2.2. Study Design.* The research protocol was approved by the Ethics Committee of the Faculty of Medicine attached to the Universidad Autónoma de Yucatán. Necessary authorizations were obtained at the following associations: Solyluna A.C., Construyendo Sonrisas: Patronato Peninsular Pro Niños con Deficiencia Mental A.C., Fundación de Orientación Holística, and Centro de Rehabilitación e Inclusión Infantil Teletón, CRIT Yucatán. The subjects were collected through nonprobability sampling by quota. The study population was divided into two groups: (1) those who had received OMT uninterruptedly in the association that they attended to for at least one year before the evaluation, on any of the physical therapy approaches (manual therapy, electrotherapy, active-assisted exercises, etc.), and (2) those who had not received any kind of OMT.

For this study, children receiving OMT attended two types of sessions in concordance with their individual therapeutic goals: passive range of motion exercises and active-assistive range of motion exercises. They received also sensory stimulation of the muscles of the face and mouth, with different textures and therapeutic devices. OMT sessions took place 2–3 times per week, with a maximum duration of 30 minutes, and were conducted by both occupational and physical therapists specializing in language and speech therapy.

A minimum attendance prerequisite was set at 80% of all OMT sessions to be classified as part of the first group. This requirement was verified by double checking the files of the participants provided by the different associations cited above. On the other side, all participants who were not able to prove the 80% minimum attendance requirement at their OMT sessions, along with those who stopped going to their physical rehabilitation center, those who received OMT for less than a year, and those whose rehabilitation center did not provide OMT, were classified at the group who did not receive OMT.

Parents or tutors who agreed that the minors participate in this study signed the informed consent and were interviewed during the days the children attended therapy in their rehabilitation centers. Assessments were conducted on the same day, with the parents present; the children's gross motor control was evaluated with the Gross Motor Function Classification System or GMFCS [15] and the feeding and swallowing skills (FSS) with the Feeding Oral Motor Scale [16]. GMFCS was used as a reference to compare the groups with high and low motor function. The Feeding Oral Motor Scale assesses qualitatively seven feeding skills and a global score (general oral motor skills), each one of the seven skills has one or more dimensions that get graded from 1 to 3 (optimal, average, and poor), and a higher score means more limitation. Table 1 illustrates the seven skills and their respective dimensions.

The body mass index (BMI) ($kg/m^2$) was used as an anthropometric guide of the children's nutritional status. To achieve this, weight measures were made with a SECA model 750 brand portable floor scale with a capacity of 150 kg and the height was determined with a SECA brand model 213 stadiometer. Anthropometric measurements were taken by the nutritionist at the physical rehabilitation center where the children attended. Once the anthropometric measurements were obtained, the BMI was calculated and classified, according to the BMI-for-age percentile charts adapted to children with CP accordingly to their gross motor level (GMFCS), elaborated by the Developmental Medicine and Child Neurology Journal [17], to determine if they classified as adequate weight, underweight, or very underweight within the characteristics of the CP population. The nutritional status was analyzed using the following cut points: very low weight with 12.8 or less, underweight from 12.9 to 14, adequate weight from 14.1 to 23, and overweight greater than 23.1.

Frequent respiratory disease variable was obtained by interviewing the tutor, and it was considered positive if, in a period of 6 months prior to the date of the study, the child had at least two of the following diseases: flu and common cold, bronchitis, pneumonia, airway infections, and acute symptoms of chronic diseases such as asthma, rhinitis, or rhinosinusitis.

*2.3. Statistics Analysis.* Result analyses were performed with the statistical package IBM SPSS, version 2.0. Student's $t$ -tests were performed to compare the scores obtained on the different scales used to assess feeding and swallowing skills (FSS). Two-proportion $Z$ tests were also performed to associate the percentages obtained within the optimal, average, and poor categories in the group that received OMT and in the one that did not. The Fisher test was used to associate nutritional status and the presence of respiratory diseases with OMT.

## 3. Results and Discussion

*3.1. Results.* This study included data from 30 children with CP (53% females and 47% males), with an average age of $8 \pm 4.07$ years. The group that had previously received OMT was conformed of 8 men and 7 women, with ages between 3 and 14 years ($8 \pm 4$). On the other hand, children without treatment were 6 men and 9 women, aged 3 to 14 years ($7 \pm 4.15$). No statistical differences were found between both groups ($p = 0.77$ and $p = 0.75$, respectively).

Table 1: Feeding oral motor scale.

| Skill | Dimensions |
|---|---|
| Posture | Head-neck control and alignment |
| | Head mobility |
| | Scapular mobility |
| | Trunk stability |
| Jaw mobility | Lateral |
| | Opening-closing |
| | Movement coordination |
| Tongue activity | Lateral |
| | Retraction |
| | Up and out movement |
| | Rest position |
| Lips | Lip seal |
| | Lip protrusion |
| | Rest position |
| Feeding behavior | Liquid suction |
| | Chewing |
| | Swallowing |
| Abnormal reflexes | Phasic biting |
| | Gagging |
| Breathing control | Breath-swallow coordination |
| General oral motor skills | — |

Initially, the two study groups, with and without OMT, are portrayed, according to the CP clinical classification and the degree of gross motor impairment. In accordance with the CP clinical classification, 67% of the population had spastic CP and 33% other classifications (ataxic 6.7%, hypotonic 13.3%, and mixed 13.3%), and according to the topographic classification, 73% had tetraplegia, 16% diplegia, and 10% hemiplegia. On the other hand, regarding the degree of gross motor impairment and according to the GMFCS scale, 63.4% of the participants were classified as levels IV and V, which correspond to the most severe level of functional limitation. The remaining 36.6% of the population was distributed between levels II and III, which refer to a mild impairment level of gross motor function. Finally, no participant was reported in level I. Table 2 describes these characteristics in the two study groups.

Subsequently, the FSS of both groups was evaluated. Of the seven FSS, differences were found in the following skills: jaw mobility, tongue activity, abnormal reflexes, and breathing control. Special attention is given to jaw mobility and tongue activity because their dimensions are closely related to the physical intervention of the OMT. The global score and the score by sections are shown in Table 3.

Regarding jaw mobility, the opening-closing skill was the one that was significant ($p = 0.039$). Qualitatively, 67% of the children who received OMT obtained an optimal jaw mobility score; in contrast, only 27% of the children without treatment obtained the same score (difference in proportions, $p = 0.028$).

Concerning the tongue activity, lateral tongue mobility was the only significant dimension ($p = 0.013$) of the four dimensions that belong to this skill. Qualitatively, 80% of the children who received OMT obtained an optimal tongue activity score and 40% of the children without treatment obtained the same score (difference in proportions, $p = 0.025$).

Next in order, the gross motor level averages were compared, classified according to the GMFCS as levels of high functionality (II and III) and levels of low functionality (IV and V). As can be seen in Table 4, significant differences were found between children with and without OMT at both levels of functionality.

Figure 1 shows the comparison between the two levels of functionality according to the GMFCS and the average score in FSS. As can be seen, in both categories, the group that did not receive OMT obtained the highest scores, indicating a greater compromise of skills.

Finally, as a complement to the assessment of FSS, an analysis of the nutritional status of the children and the frequency with which they contract respiratory diseases was carried out. These are key signs in determining the impact of the FSD.

For the analysis of the nutritional status, the comparison of the BMI between the groups with and without OMT was made; according to the cut of the percentile curves, a BMI greater than 14 kg/m2 indicates a normal weight and a lower BMI would correspond to low or very low weight. A significant difference ($p = 0.004$) was observed in the BMI of the children who did receive treatment ($15.8 \pm 2.21$) compared to the BMI of those who did not receive it ($13.22 \pm 2.37$). Likewise, 93% of the children who received OMT were classified to have normal weight and only 7% were underweight. In contrast, only 54% of the children who did not receive OMT had a normal weight, while 13% and 33% manifested as being underweight and very underweight, respectively. Receiving treatment corresponded significantly to normal weight ($p = 0.035$).

Regarding the frequency with which children with CP contract respiratory diseases, a significant association was found with those not receiving OMT ($p = 0.035$).

## 4. Discussion

The main finding of this study was to demonstrate that regardless of the characteristics of the OMT, the children who had received it, at least during the last year, showed better levels of FSS compared to those children who did not receive it. The children who received OMT showed better scores in 4 of the 7 FSS: jaw mobility, tongue activity, abnormal reflexes, and breathing control. It is important to highlight that better scores in general oral motor skills were also reported. These skills were evaluated by a rehabilitation therapist in a blinded way, who did not know that the child had received or not the OMT, which improves the accuracy of the results.

Improvement in jaw stabilization found on trial groups with mouth control training indicates the beneficial effect of OMT [9]. This study showed that jaw mobility, including coordination, lateralization, and opening-closing of the jaw, obtained better scores in children with OMT. Even though

Table 2: Description of PC types and motor impairment in the groups with and without OMT.

| Groups | Clinical type: *N* | Topographic type: *N* | Gross motor level: *N* |
|---|---|---|---|
| With OMT, *N*:15 | Ataxic: 2<br>Spastic: 9<br>Hypotonic: 2<br>Mixed: 2 | Diplegia: 4<br>Hemiplegia: 1<br>Tetraplegia: 10 | High function: 5<br>Low function: 10 |
| Without OMT, *N*: 15 | Spastic: 11<br>Hypotonic: 2<br>Mixed: 2 | Diplegia: 1<br>Hemiplegia: 2<br>Tetraplegia: 12 | High function: 6<br>Low function: 9 |

This chart shows that both groups had similar PC types and motor conditions (chi squared, $p = 0.7$).

Table 3: Feeding and swallowing skills in Yucatecan children with CP.

| Skills | With OMT | Without OMT | *p* |
|---|---|---|---|
| Posture | 6.00 ± 0.640 | 7.40 ± 0.804 | 0.184 |
| Jaw mobility | 4.27 ± 0.358 | 5.47 ± 0.350 | 0.023* |
| Tongue activity | 5.73 ± 0.228 | 6.87 ± 0.496 | 0.047* |
| Lips | 4.13 ± 0.307 | 5.00 ± 0.352 | 0.074 |
| Feeding behavior | 3.60 ± 0.190 | 4.33 ± 0.410 | 0.116 |
| Abnormal reflexes | 0.00 | 0.27 ± 0.118 | 0.032* |
| Breathing control | 1.00 | 1.27 ± 0.118 | 0.032* |
| General oral motor skills | 24.73 ± 1.240 | 30.60 ± 2.190 | 0.027* |

Values represent mean ± standard deviation. Student's *t*-test for independent samples. *Significant difference.

abnormal oral reflexes have been observed in children with CP [18], such as phasic biting and gagging, little or no research exists that analyzes those reflexes with the OMT. However, in this study, it was found that the group with treatment had a lower presence of abnormal reflexes, compared to the group with no treatment.

Authors, such as Harden and Rydell [19], had already reported an improvement in tongue activity in children who received OMT, since they performed better according to the scale of severity of tongue protrusion, after 5 years of treatment. Likewise, by promoting proper tongue management, other problems such as tooth misalignment, excess salivation, and atypical swallowing are prevented, while other skills such as language and socialization are benefited [20].

On the other hand, other authors [21] have been interested in the effect of OMT to control breathing during feeding, improving control and coordination of swallowing and breathing, avoiding episodes of coughing or choking. However, due to the lack of a timely treatment to address the incoordination between suction and breathing, a nasogastric tube is frequently chosen, and if the weight gain is inadequate, a gastrostomy might proceed; in this sense, the importance of respiration is directly and indirectly reflected in the nutritional status; however, this point will be discussed later.

Another important finding of this study was the significant differences between children with and without OMT in the two groups of GMFCS, showing that regardless of the level of motor functionality, the OMT improves the FSS and could have even more impact in the low-function group. Some authors have shown that children with gross motor disorders tend to have a higher prevalence of FSD [22]. Other studies analyzed the relationship between the GMFCS level and the complications associated with FSD and found that for most children at level V, it is not safe to eat either solid or liquid textures, so they use semisolid textures [23, 24]. Furthermore, the benefit of OMT in children with CP may also be reflected in other areas, for example, in visual-motor coordination and language [25]; however, these functions were not explored in this study.

As previously discussed, a secondary objective of this study was to evaluate the relationship between OMT and the nutritional status of children, as well as the frequency with which they contracted respiratory diseases. Regarding the first point, it was found that the children who received OMT had higher levels of normal weight since a child who eats adequately can have a body status appropriate for his age and sex, thereby improving the chances of better function and growth. On the contrary, low weight and malnutrition favor states of immunosuppression and a greater predisposition to other diseases, which can complicate the prognosis and decrease the quality of life of children with CP. This is consistent with different studies on nutrition in children with CP, which state that eating disorders represent an important predictor of poor health, expressed in nutritional deficiencies and poor quality of life [21], which is related to the next point: the frequency of respiratory diseases. The parents of the children who had received OMT in the last year stated that their children had presented fewer events of respiratory infections, which may correspond to better FSS.

This study does not take into consideration a follow-up at home with the parents of children with OMT. Nevertheless, additional instructions regarding postures during feeding, nutrition, and adaptations were provided to the parents and they actively participated in the OMT sessions with their kids.

Also, it is important to remark that the heterogeneity of techniques of treatment, along with the different patients' diagnoses and prognoses, prevents the researchers from including only participants who received the same type of OMT. For example, some children received neuromuscular electrostimulation once a month.

Table 4: Relation between OMT and gross motor.

| Gross motor level (GMFCS) | With OMT | Without OMT | $p$ |
|---|---|---|---|
| High function levels (II and III) | $20.80 \pm 1.304$ ($n = 5$) | $22.33 \pm 1.033$ ($n = 6$) | 0.028* |
| Low function levels (IV and V) | $26.70 \pm 4.715$ ($n = 10$) | $36.11 \pm 6.314$ ($n = 9$) | 0.003* |

Values represent mean ± standard deviation, while the correspondent $n$ is in parenthesis. Student's $t$-test for independent samples.

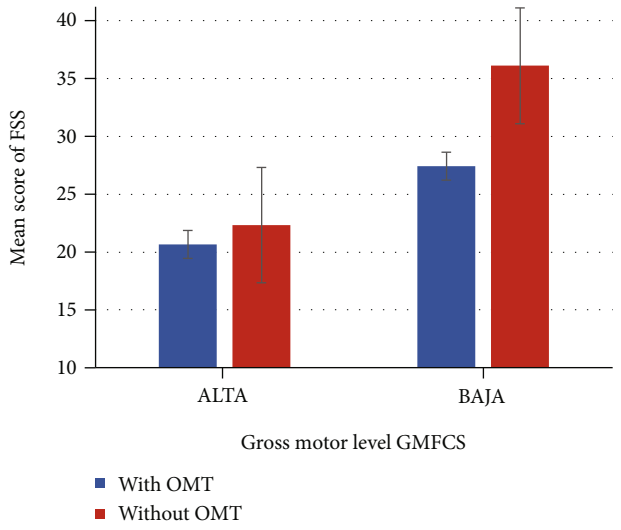


Figure 1: Mean score of FSS with respect to receiving OMT or not in two groups of gross motor level (high or low). A high score in FSS indicates more limitation at the skill, therefore, less desirable.

Additionally, respiratory physiotherapy was not defined as a variable of the OMT for the purposes of this study.

Also, since the results were based on a limited number of subjects and due to the lack of studies in the field of OMT efficacy in children with CP, the results of this study must be treated with caution.

Nevertheless, the above-cited findings are substantial and should encourage further studies on a larger scale. One possibility could be exploring the clinical effects of OMT treatment protocols on the dysarthria presented in CP patients. Finally, an instrumental dynamic study such as VFSS before and after OMT and respiratory therapy regimens to note more objectively the effects of feeding and swallowing parameters could be of great relevance.

## 5. Conclusions

Children who received CP during the last OMT, in some of its modalities, showed better FSS, regardless of their level of gross motor functionality, as well as better indicators of nutritional status and less frequency of respiratory diseases, which results in important benefits for the health of this population group.

This is the reason why we propose that OMT be included in the rehabilitation intervention schemes for children with CP since the benefits indicated in this study highlight the importance of FSS in the health and quality of life of children with CP. It would also be important to evaluate the different OMT techniques and establish the clinical benefits associated with each of them and standardize a management scheme for children with CP.

## Data Availability

The datasets were obtained by the authors.

## Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Hindawi
Behavioural Neurology
Volume 2021, Article ID 6696806, 10 pages
https://doi.org/10.1155/2021/6696806

*Research Article*

# Synergistic Effects of Aldehyde Dehydrogenase 2 Polymorphisms and Alcohol Consumption on Cognitive Impairment after Ischemic Stroke in Han Chinese

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Received 1 April 2021; Revised 16 May 2021; Accepted 7 June 2021; Published 25 June 2021

Academic Editor: Lambros Messinis



Aldehyde dehydrogenase 2 (*ALDH2*) polymorphisms are related to both stroke risk and alcohol consumption. However, the influence of *ALDH2* polymorphisms and alcohol consumption on cognitive impairment after ischemic stroke remains unknown, as do the possible mechanisms. We enrolled 180 Han Chinese ischemic stroke patients from four community health centers in Bengbu, China. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), and two different MoCA cutoff scores were used to define cognitive impairment in ischemic stroke patients. The *ALDH2* genotypes were determined using polymerase chain reaction and direct sequencing. To assess the associations of *ALDH2* polymorphisms and alcohol consumption with cognitive impairment after ischemic stroke, we performed binary logistic regression analysis with odds ratios. We revealed that individuals with the *ALDH2* wild-type genotype were more likely to have high MoCA scores than those with the mutant and heterozygous types ($p = 0.034$). In addition, using two MoCA cutoff scores, the percentage of moderate to excessive alcohol consumption in the cognitive impairment group was higher than that in the nonimpairment group ($p = 0.001$). The levels of 4-hydroxy-2-nonenal ($p = 0.001$) and swallowing function ($p = 0.001$) were also higher in the cognitive impairment group than in the nonimpairment group. Moreover, after adjusting for other potential risk factors, *ALDH2* polymorphisms and alcohol consumption had a significant synergistic effect on cognitive impairment ($p = 0.022$). Specifically, the *ALDH2* $*$ *2* mutant allele and higher alcohol consumption were associated with cognitive impairment and swallowing ability after ischemic stroke. Targeting ALDH2 may be a useful biomarker for cognitive rehabilitation following ischemic stroke.

## 1. Introduction

Stroke is an important problem in public health and is the leading cause of adult disability worldwide [1, 2]. It has been reported that approximately 15 million people per year have a stroke [3]. Most patients experience some disturbance in cognitive function following stroke [4], and cognitive function is a significant focus in stroke rehabilitation [5]. Alcohol consumption, which is common worldwide, affects the development of stroke and cognitive performance [6, 7]. Epidemiological evidence has revealed that excessive drinking is a major risk factor for all stroke subtypes, but especially for ischemic stroke [8, 9]. Additionally, some cohort studies have suggested that light to moderate drinking may have a protective effect on cardiovascular disease and ischemic stroke [9, 10]. In contrast, more recent studies have indicated that alcohol consumption is roughly linearly associated with stroke risk [11, 12]. However, a U-shaped relationship has also been reported between regular alcohol consumption and cognitive function in several major epidemiological studies [13]; thus, the relationship between alcohol consumption and cognitive impairment after ischemic stroke remains uncertain.

Alcohol metabolism represents a key biological determinant that can impact drinking behavior. Aldehyde dehydrogenase 2 (ALDH2) is the primary enzyme involved in this metabolic process [14]. Previous research has examined the potential effects of ALDH2 on alcohol consumption and health outcomes. However, the relationship between ALDH2, alcohol consumption, and cognitive function in patients with ischemic stroke is unclear. The main function of ALDH2 is to detoxify acetaldehyde, which is a toxic chemical product of ethanol metabolism [15]. Moreover, ALDH2 also removes other toxic aldehydes, such as 4-hydroxy-2-nonenal (4-HNE). As a potential substrate of ALDH2, 4-HNE is commonly considered a specific marker of ischemic stroke injury [15, 16].

ALDH2 is abundant in the brain, heart, lungs, and other organs with high mitochondrial contents [17, 18]. The *ALDH2* gene consists of 13 exons and 12 introns. In exon 12, a polymorphism exists, in the form of a G-to-A missense mutation. The glutamate at position 504 is substituted by lysine (Glu504Lys). This polymorphism is also known as rs671, or the *ALDH2 ∗ 2* form, while the more common wild-type form is known as *ALDH2 ∗ 1*. There are thus three possible allele combinations in the population: wild-type (∗1/∗1), heterozygote (∗1/∗2), and mutant (∗2/∗2) [19, 20]. Approximately 40% of the East Asian population carries an *ALDH2 ∗ 2* mutant allele, with a resulting marked reduction in enzymatic activity [15]. Recent studies have reported that the Glu504Lys polymorphism may affect ischemic stroke risk in the Han Chinese population and that carriers of the *ALDH2 ∗ 2* allele have increased 4-HNE levels after stroke [21]. However, there has been little previous research into the association between *ALDH2* genotypes and cognitive impairment after ischemic stroke.

Therefore, the aim of this study was to evaluate the association of *ALDH2* genotypes and alcohol consumption with cognitive function after ischemic stroke. Cognitive function can be tested briefly using the Montreal Cognitive Assessment (MoCA), and this test is recommended for screening cognitive impairment in patients with ischemic stroke [22]. In many previous studies, cognitive impairment has been defined as a MoCA score < 26 [23]. However, some researchers have recommended that a MoCA cutoff score of 22/23 points might be more suitable for detecting cognitive impairment [24]. In addition, swallowing deficits are also commonly reported in patients with ischemic stroke [25], and cognitive dysfunction is related to dysphagia [26]. In the present study, we used these two different MoCA cutoff scores to investigate the relationship between alcohol consumption, 4-HNE levels, swallowing function, and cognitive impairment after ischemic stroke, respectively. We further investigated the synergistic effects of *ALDH2* genotype and alcohol consumption on the MoCA score and swallowing ability in ischemic stroke patients. Finally, we sought to explore the underlying mechanisms that might influence these associations.

## 2. Methods

*2.1. Patients.* From June 2015 through August 2015, patients with ischemic stroke from four community health centers located in the Longzihu District of Bengbu (Anhui Province, China) were recruited in our study. We visited each community and held a free health checkup for participants. Each participant completed a self-reported questionnaire relating to their lifestyle and medical history, including information on prior stroke and baseline disease status. The inclusion criteria for ischemic stroke patients were as follows: (i) stroke diagnosis as per the revised diagnostic criteria of the 4th National Cerebrovascular Disease Conference in China [27], (ii) stroke diagnosis based on computed tomography or magnetic resonance imaging brain scans, (iii) within 3 months after stroke onset, (iv) permanent residents of Han Chinese ethnicity in selected communities, and (v) informed consent provided. The exclusion criteria were as follows: (i) previous history of cerebral vascular malformation, transient ischemic attack, intracranial hemorrhage, stroke mimics (i.e., seizures or migraines), or neurological deficits; (ii) previous history of bleeding diathesis, anticoagulation therapy, illicit drug use, or serious medical illness; (iii) previous history of illiteracy or any major mental or physical condition that may interfere with cognitive assessments; and (iv) a diagnosis of coronary artery disease [19, 22, 28].

Data were initially obtained from 200 participants. We excluded patients who were unable to participate in the interview because of serious cognitive impairment ($n = 5$) and those with missing medical records ($n = 4$). We also excluded subjects who had missing information regarding alcohol habits, such as alcohol status and the amount and frequency of alcohol consumption ($n = 7$), and regarding recurrence and death ($n = 4$). Thus, a total of 180 patients with ischemic stroke were enrolled in this study. A detailed flowchart showing participant selection is provided in Figure 1.

*2.2. Demographic and Clinical Characteristics and Measurements.* We obtained patient demographic information from patients' medical charts and self-reported data. According to the medical charts, patients were divided into two subtypes using a simple clinical scheme with the Oxfordshire Community Stroke Project (OCSP) classification and included the following: posterior circulation infarction (PCI) and anterior circulation infarction (ACI) [29]. In the PCI group, the infarcts involved the brainstem, posterior cerebral artery area, thalamus, or cerebellum; in the ACI group, the infarcts occurred in the region of the middle cerebral artery, anterior cerebral artery, or anterior choroidal artery [30].

After fasting for 8 to 12 hours, we measured each patient's blood pressure, height, and weight and calculated their body mass index (BMI). In addition, fasting venous blood samples were collected at approximately the same time of day, in the morning, to minimize diurnal variations [31]. Each blood sample was drawn into a tube containing ethylenediaminetetraacetic acid as an anticoagulant and a tube without anticoagulant. The obtained plasma and serum were preserved at -80°C until assays were performed. Routine blood and biochemistry tests were analyzed, including fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). This part of

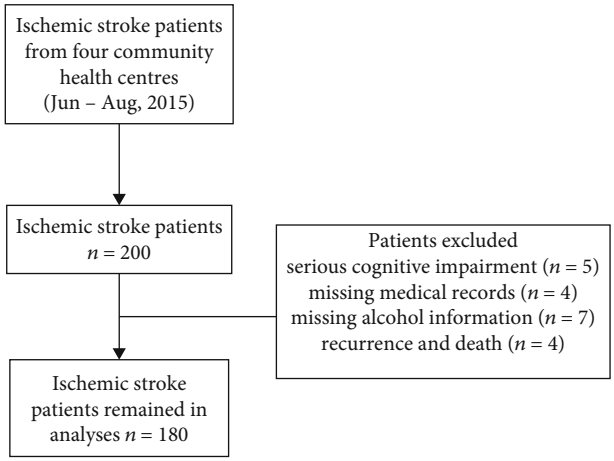


Figure 1: Flowchart of the participant selection process.

the study was approved by the ethics committee of Bengbu Medical College. The cognitive assessments were conducted at the same time as the blood samples were taken.

*2.3. Cognitive Assessments.* The MoCA is a cognitive screening tool that can be used to distinguish healthy cognitive aging from mild cognitive impairment [32]. It is simple to conduct, sensitive, and valid. Since its introduction into clinical practice, it has been repeatedly demonstrated to be suitable for the initial assessment of mental status and for follow-up assessments [33]. The MoCA was administered by trained physicians in each community.

The MoCA comprises eight subtests that involve visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation with respect to time and place. MoCA scores range from 0 to 30. A higher score indicates better cognitive performance [34, 35]. With a cutoff of 26 (which we used as Method 1 in our study), the sensitivity and specificity of MoCA have been reported as 90% and 87%, respectively, when administered to screen patients with mild cognitive impairment in Canada [32]. However, subsequent clinical studies have demonstrated that some patients with normal cognitive ability have MoCA scores below 26 [36]. The MoCA cutoff scores of ischemic stroke patients by the educational level have been reported as follows: 24/25 for individuals with ≥7 years of education, 19/20 for individuals with 1 to 6 years of education, and 13/14 for illiterate individuals. Therefore, we also used a cutoff point of 22/23 (which we used as Method 2 in our study) for MoCA scores [24, 31, 37].

*2.4. Water-Swallowing Test.* The water-swallowing test (WST) is frequently used in clinical practice as a functional assessment to evaluate swallowing function [38]. Swallowing performance was assessed with the 30 mL water swallowing test which is cheap, easy to use, and with the highest reliability [39]. A total of 30 mL water was put on a plastic cup. The patient was ordered to drink the water "as quickly as comfortably possible" in an upright seated position. The time to drink and presence or absence of coughing were recorded. The results included the following five levels: level I (drink once, no coughing), level II (drinking more than two times of interruption, no coughing), level III (drinking once, with coughing), level IV (drinking more than two times of interruption, with coughing), and level V (coughing frequently and cannot drink the water successfully). After examination, swallowing ability was classified as normal (level I within 5 s), possible abnormality (level I over 5 s or level II), and abnormality (levels III to V). Possible abnormality and abnormality are considered dysphagia [39].

Table 1: Demographics of the study participants.

| Characteristics | ALDH2 genotypes | | $t$/chi square | $p$ value |
|---|---|---|---|---|
| | ∗1/∗1 ($n = 87$) | ∗1/∗2+∗2/∗2 ($n = 93$) | | |
| Age (years) | 67.92 ± 8.02 | 69.88 ± 9.53 | 1.490 | 0.138 |
| Males, $n$ (%) | 38 (43.7%) | 49 (52.7%) | 8.536 | 0.003 |
| Education | | | 7.013 | 0.071 |
| <6 years | 18 (20.7%) | 22 (23.7%) | | |
| 6-9 years | 27 (31.0%) | 19 (20.4%) | | |
| 9-12 years | 21 (24.1%) | 37 (39.8%) | | |
| >12 years | 21 (24.1%) | 15 (16.1%) | | |
| Alcohol consumption | | | 12.464 | 0.006 |
| Nondrinkers | 12.6% | 21.5% | | |
| Light drinkers | 8.0% | 22.6% | | |
| Moderate drinkers | 36.8% | 30.1% | | |
| Excessive drinkers | 42.5% | 25.8% | | |

Continuous variables are expressed as the mean ± standard deviation when normally distributed, and categorical variables are expressed as percentages.

*2.5. Alcohol Consumption Measurements.* Data regarding alcohol consumption were collected via a self-administered questionnaire [40]. The questionnaire included a range of drinking variables in the past 12 months before the stroke. The type of alcohol (liquor, beer, or wine), quantity of consumption, and frequency of consumption (never or occasionally, daily, weekly, or monthly) were all assessed. The average daily intake of absolute alcohol was estimated based on the quantity and frequency of consumption. The content of ethanol (pure alcohol) was assumed to be 15.1 g for a drink of liquor, 13.2 g for a can of beer, and 10.8 g for a standard glass of wine [41, 42]. For each participant, total ethanol intake was converted to standard units per week (1 unit = 8 g ethanol). Each participant's drinking status was then classified as one of four distinct categories: nondrinker, light drinker, moderate drinker, or excessive drinker [41]. Nondrinkers consumed <1 unit of ethanol per week. Light drinkers consumed 1-10 units/week for men and 1-7 units/week for women. Moderate drinkers consumed 11-21 units/week for men and 8-14 units/week for women. Excessive drinkers consumed >21 units/week for men and >14 units/week for women.

*2.6. 4-HNE Concentration Measurements.* The plasma levels of 4-HNE were estimated using ELISA kits (Elabscience Biotechnology, Wuhan, China) according to the manufacturer's instructions [21].

*2.7. ALDH2 Genotyping Measurements.* Genomic DNA samples were obtained from blood samples using commercial DNA extraction kits (Tiangen Biotech, Beijing, China). The primer sequences were as follows: forward primer, 5′-GTCAACTGCTATGATGTGTTTGG-3′ and reverse primer, 5′-CCACCAGCAGACCCTCAAG-3′. The 50 $\mu$L polymerase chain reaction (PCR) mixture consisted of 2 $\mu$L DNA template, 2 $\mu$L forward and 2 $\mu$L reverse primers, 25 $\mu$L TaqMan Master Mix, and 19 $\mu$L double-distilled $H_2O$. The PCR was conducted with predenaturation for 3 min at 94°C, followed by 35 cycles of amplification (94°C for 45 s, 53°C for 30 s, and 72°C for 45 s), and extension for 5 min at 72°C [20]. The PCR products were purified using commercial kits (Axygen Biosciences, Corning, NY, USA) and sent to GenScript Corporation (Nanjing, China) for sequencing.

*2.8. Statistical Analyses.* The results of continuous variables are presented as the mean ± standard deviation (SD), whereas the results of categorical variables are expressed as numbers of patients and percentages. Two-tailed Student's *t*-test or one-way ANOVA was performed for continuous variables, and the $\chi^2$ test was performed for categorical variables. Binary logistic regression analysis was performed to determine the associations of *ALDH2* polymorphisms and alcohol consumption with cognitive impairment and swallowing ability after ischemic stroke in a Han Chinese population by estimating the odds ratios (ORs) with 95% confidence intervals (CIs) [43]. We used two different cognitive impairment assessment methods (Method 1 and Method 2) to estimate the correlations between *ALDH2* polymorphism, alcohol consumption, and cognitive impairment. All missing values of predictors were imputed. Statistical analyses were conducted using SPSS version 24.0 software (IBM Corporation, Chicago, USA). All $p$ values of less than 0.05 were taken as statistically significant.

## 3. Results

*3.1. Baseline Characteristics.* Table 1 shows the demographic characteristics of all participants, grouped by ALDH2 polymorphism. We combined the heterozygotes (ALDH2 ∗ 1/∗2) and mutant homozygotes (ALDH2 ∗ 2/∗2) into one category and compared them with the wild-type homozygotes (ALDH2 ∗ 1/∗1) in our analyses. There were no significant differences between the two categories in age or education. However, the levels of alcohol consumption were significantly higher in the ALDH2 wild-type genotype group than in the mutant and heterozygous genotype group ($p = 0.006$). We further compared alcohol consumption between two ALDH2 genotypes by gender; the results showed that there was no statistical difference between genotype and alcohol consumption in males. However, the levels of alcohol consumption were significantly higher in the ALDH2 wild-type genotype group than in the mutant and heterozygous genotype group in females ($p = 0.001$, Supplementary Table 1).

*3.2. Clinical Characteristics.* The clinical characteristics of participants according to ALDH2 polymorphism are shown in Table 2. There were no significant differences between the two groups in BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), or FPG, TG, HDL-C, or LDL-C levels. However, 4-HNE levels were higher in patients with mutant alleles (13.42 ± 2.11 ng/L) than in patients with wild-type alleles (12.18 ± 1.94 ng/L; $p = 0.001$), whereas TC levels were lower in patients with mutant alleles (5.62 ± 1.40 mmol/L) than in patients with wild-type alleles (6.16 ± 1.94 mmol/L; $p = 0.037$).

Table 2: Baseline characteristics of ischemic stroke patients with different *ALDH2* genotypes.

| Characteristics | ALDH2 genotypes | | $t$ | $p$ value |
|---|---|---|---|---|
| | ∗1/∗1 ($n = 87$) | ∗1/∗2+∗2/∗2 ($n = 93$) | | |
| BMI (kg/m$^2$) | 24.46 ± 2.91 | 25.22 ± 2.67 | 1.821 | 0.070 |
| SBP (mmHg) | 137.25 ± 20.10 | 142.65 ± 24.83 | 1.595 | 0.113 |
| DBP (mmHg) | 81.95 ± 9.24 | 82.09 ± 8.84 | 0.098 | 0.922 |
| FPG (mmol/L) | 7.31 ± 1.91 | 7.58 ± 1.98 | 0.911 | 0.363 |
| TC (mmol/L) | 6.16 ± 1.94 | 5.62 ± 1.40 | 2.106 | 0.037 |
| TG (mmol/L) | 2.13 ± 0.65 | 1.50 ± 0.65 | 1.252 | 0.214 |
| HDL-C (mmol/L) | 1.18 ± 0.37 | 1.15 ± 0.32 | 0.583 | 0.561 |
| LDL-C (mmol/L) | 2.51 ± 0.96 | 2.54 ± 0.75 | 0.234 | 0.815 |
| 4-HNE (ng/mL) | 12.18 ± 1.94 | 13.42 ± 2.11 | 4.096 | 0.001 |

Continuous variables are expressed as the mean ± standard deviation when normally distributed, and categorical variables are expressed as percentages. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; 4-HNE: 4-hydroxy-trans-2-nonenal.

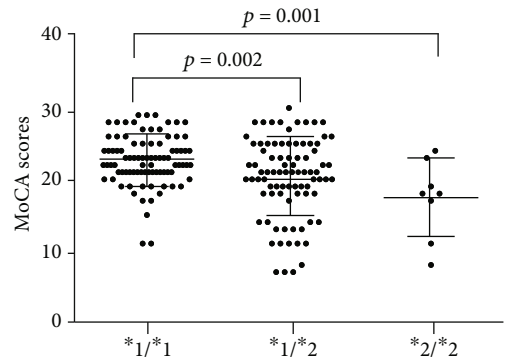


Figure 2: Comparison of Montreal Cognitive Assessment (MoCA) scores of ischemic stroke patients grouped by *ALDH2* genotype.

*3.3. Analysis of Cognitive Performance in Subjects with Different ALDH2 Genotypes.* MoCA was used in ischemic stroke patients as a dependent variable to assess the extent of early vascular cognitive dysfunction. We compared the MoCA scores of three genotypes by analysis of variance ($F = 8.643$, $p = 0.0003$). Figure 2 shows that the MoCA scores of the *ALDH2* wild-type genotype group ($n = 87$, 22.64 ± 3.55) were higher than those of the heterozygous group ($n = 85$, 20.28 ± 5.52; $p = 0.001$). The MoCA scores of the

Table 3: Comparison of alcohol consumption between the cognitive impairment and nonimpairment groups according to two different Montreal Cognitive Assessment (MoCA) cutoff scores.

| Alcohol consumption | Method 1 | | Method 2 | |
|---|---|---|---|---|
| | Impairment | Nonimpairment | Impairment | Nonimpairment |
| Nondrinkers | 21 (13.4%) | 10 (43.5%) | 12 (9.9%) | 19 (32.2%) |
| Light drinkers | 24 (15.3%) | 4 (17.4%) | 18 (14.9%) | 10 (16.9%) |
| Moderate drinkers | 52 (33.1%) | 8 (34.8%) | 44 (36.4%) | 16 (27.1%) |
| Excessive drinkers | 60 (38.2%) | 1 (4.3%) | 47 (38.8%) | 14 (23.7%) |
| Chi square | 17.419 | | 15.238 | |
| $p$ value | 0.001 | | 0.002 | |

Method 1: MoCA cutoff score of 26. Method 2: MoCA cutoff score of 23.

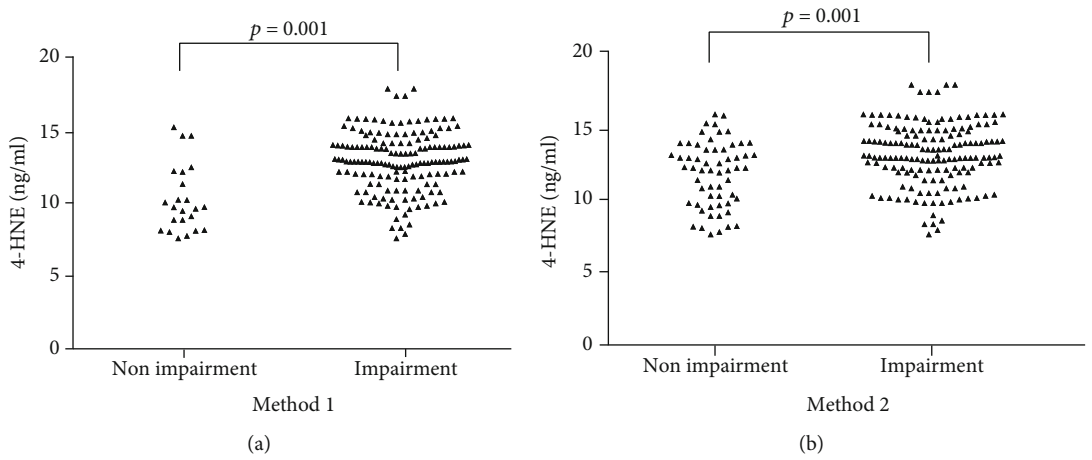


Figure 3: Comparison of 4-hydroxy-trans-2-nonenal (4-HNE) levels between the cognitive impairment and nonimpairment groups according to two different Montreal Cognitive Assessment (MoCA) cutoff scores: (a) score of 26; (b) score of 23.

*ALDH2* wild-type genotype group (22.64 ± 3.55) were higher than that of the mutant genotype group ($n = 8$, 17.25 ± 5.45; $p = 0.002$). And there was no difference between the heterozygous and mutant genotype groups ($p > 0.05$) (Figure 2).

*3.4. Association of Alcohol Consumption and 4-HNE Levels with Cognitive Impairment.* We used two different cognitive impairment assessment methods to compare alcohol consumption between the cognitive impairment and nonimpairment groups (Table 3). For both of the MoCA cutoff scores, the percentage of moderate to excessive alcohol consumption was higher in the cognitive impairment group than in the nonimpairment group. According to the MoCA subscores of visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation, MoCA subscores were compared with alcohol consumption in two *ALDH2* genotypes. Intergroup differences were assessed using the single factor analysis of variance. Among the seven subscores, we found that two subscores (language and delayed recall) have a significant difference in alcohol consumption using univariate analysis (Supplementary Table 2).

We also used the two different MoCA cutoff scores to compare 4-HNE levels between the cognitive impairment and nonimpairment groups (Figure 3(a)). With a cutoff score of 26, the levels of 4-HNE were higher in the cognitive impairment group (12.94 ± 2.01, $n = 157$) than in the nonimpairment group (10.29 ± 2.29, $n = 23$). Furthermore, when we considered MoCA scores and educational levels of the ischemic stroke patients, with a cutoff score of 23 (Figure 3(b)), the levels of 4-HNE were also higher in the cognitive impairment group (12.98 ± 2.14, $n = 121$) than in the nonimpairment group (11.81 ± 2.22, $n = 59$).

*3.5. Association between Swallowing Function and Cognitive Impairment.* We used two different cognitive impairment assessment methods, to compare swallowing levels between the cognitive impairment and nonimpairment groups (Table 4). For both of the MoCA cutoff scores, the level of swallowing function was higher in the cognitive impairment group than in the nonimpairment group.

*3.6. Separate Effects of ALDH2 Polymorphisms and Alcohol Consumption on Cognitive Impairment.* To test the possible association of *ALDH2* polymorphism and alcohol consumption with cognitive impairment, we assessed the separate effects of *ALDH2* polymorphism and alcohol consumption on cognitive impairment in ischemic stroke patients. The association between *ALDH2* polymorphisms and cognitive impairment risk in ischemic stroke patients is shown in Table 5. At a cutoff MoCA score of 26, participants carrying the mutant *ALDH2* allele had a higher risk of cognitive impairment (OR = 3.29, 95%CI = 1.03 – 10.50, $p < 0.05$).

Table 4: Comparison of swallowing function between the cognitive impairment and nonimpairment groups according to two different MoCA cutoff scores.

| Swallowing | Method 1 | | $p$ | Method 2 | | $p$ |
|---|---|---|---|---|---|---|
| | Impairment | Nonimpairment | | Impairment | Nonimpairment | |
| Level I | 9 (5.7%) | 23 (100.0%) | 0.001 | 0 (0.0%) | 32 (54.2%) | 0.001 |
| Level II | 44 (28.0%) | 0 (0.0%) | | 17 (14.0%) | 27 (45.8%) | |
| Level III | 53 (33.8%) | 0 (0.0%) | | 53 (43.8%) | 0 (0.0%) | |
| Level IV | 29 (18.5%) | 0 (0.0%) | | 29 (24.0%) | 0 (0.0%) | |
| Level V | 22 (14.0%) | 0 (0.0%) | | 22 (18.2%) | 0 (0.0%) | |

Table 5: Adjusted odds ratios (95% confidence intervals)[a] for the separate effects of *ALDH2* polymorphism and alcohol consumption on cognitive impairment in ischemic stroke patients.

| | Method 1 | Method 2 |
|---|---|---|
| ALDH2 genotypes | | |
| ∗1/∗1 | Ref | Ref |
| ∗1/∗2+∗2/∗2 | 3.29 (1.03-10.50)* | 2.65 (1.19-5.92)* |
| Alcohol consumption | | |
| Nondrinkers | Ref | Ref |
| Light drinkers | 0.59 (0.16-0.89)# | 0.68 (0.33-0.89)# |
| Moderate drinkers | 0.77 (0.21-1.06) | 1.08 (0.83-2.19) |
| Excessive drinkers | 1.22 (1.16-1.49)# | 1.78 (1.03-2.15)# |

[a]Models were adjusted for age, gender, and education. *$p < 0.05$ vs. ALDH2 wild-type genotype group (ALDH2 ∗ 1/∗1). #$p < 0.05$ vs. nondrinkers.

Similarly, at a cutoff MoCA score of 23, participants carrying the mutant *ALDH2* allele also had a higher risk of cognitive impairment (OR = 2.65, 95%CI = 1.19 – 5.92, $p < 0.05$).

Further analysis of these results revealed a clear association between alcohol consumption and cognitive impairment risk in ischemic stroke patients. At a MoCA cutoff score of 26, there was an OR of 0.59 (95%CI = 0.16 – 0.89) in light drinkers and an OR of 1.22 (95%CI = 1.16 – 1.49) in excessive drinkers compared with nondrinkers. The OR values using a MoCA cutoff score of 23 were similar to the values using a cutoff score of 26.

*3.7. ORs of Alcohol Consumption on Cognitive Impairment, Stratified by ALDH2 Polymorphism.* Table 6 shows the ORs of alcohol consumption on cognitive impairment, stratified by ALDH2 polymorphism, after taking into account other potential risk factors. At a MoCA cutoff score of 26, the multivariate OR of cognitive impairment risk was 7.75 (95% CI: 1.03–113.78) for the *ALDH2* wild-type genotype in excessive drinkers compared with nondrinkers. In patients with the *ALDH2* heterozygous group, the multivariate OR (95% CI) of cognitive impairment risk compared with nondrinkers was 10.95 (1.04-114.88) in moderate drinkers. The OR values had a similar trend using a cutoff MoCA score of 23. However, in patients with the *ALDH2* heterozygous group, the multivariate OR (95% CI) of cognitive impairment risk compared with nondrinkers was 13.74 (1.96-96.51) in light drinkers, 22.36 (3.69-135.54) in moderate drinkers, and 20.93 (2.77-158.45) in excessive drinkers.

## 4. Discussion

Previous studies have revealed that *ALDH2* polymorphisms are closely related to the incidence of ischemic stroke. The current study was the first case-cohort study describing the effects of *ALDH2* polymorphisms and alcohol consumption on cognitive impairment after ischemic stroke. We demonstrated that *ALDH2* polymorphisms and alcohol consumption had a synergistic effect on cognitive impairment, even after taking other potential risk factors into account (age, gender, education, and subtype). Our results indicate that the association between alcohol consumption and cognitive impairment is stronger in the *ALDH2* heterozygous group than in the wild-type genotype group, as well as with swallowing ability.

Cognitive impairment after stroke can affect the quality of life and long-term prognosis (higher mortality and more disability) of stroke survivors [44]. Several studies have confirmed that the common functional single nucleotide polymorphism (SNP) in exon 12 of *ALDH2* is a risk indicator for ischemic stroke [21]. SNPs are the most abundant and stable genetic variations that exist in genomes [45, 46]. In the present study, the *ALDH2 ∗ 2* polymorphism was associated with cognitive impairment after ischemic stroke, although there was a lack of evidence of this in previous studies. Our data revealed that patients in the *ALDH2* wild-type genotype group were significantly more likely to have higher MoCA scores than patients in the mutant and heterozygous genotype group, which suggests that the *ALDH2 ∗ 2* polymorphism is associated with cognitive impairment after stroke.

The MoCA can be used as a dependent variable to assess the extent of early cognitive dysfunction [22]. In previous studies, cognitive impairment was defined by a MoCA cutoff score of <26 [23, 32]. However, some researchers have recommended that a cutoff score of 22/23 points might be more suitable to detect cognitive impairment [24, 31, 37]. To test the possible association between *ALDH2* polymorphisms and cognitive impairment in patients with ischemic stroke, we therefore used two different MoCA cutoff scores to investigate interaction effects. We found that the *ALDH2* mutant allele carried a higher risk of cognitive impairment using both MoCA cutoff scores. Furthermore, 4-HNE levels were higher in the cognitive impairment group than in the nonimpairment group using both MoCA cutoff scores.

Several studies have demonstrated that 4-HNE is a potential substrate for ALDH2. The levels of 4-HNE are

Table 6: Multivariate odds ratios (95% confidence intervals)[a] for alcohol consumption on cognitive impairment in stroke patients, stratified by *ALDH2* polymorphism.

| ALDH2 genotypes | Alcohol consumption | Method 1 | Method 2 |
|---|---|---|---|
| ∗1/∗1 | Nondrinkers | Ref | Ref |
| | Light drinkers | 1.75 (0.20-15.19) | 0.45 (0.05-3.91) |
| | Moderate drinkers | 2.97 (0.60-14.68) | 2.43 (0.54-11.02) |
| | Excessive drinkers | 7.75 (1.03-113.78)* | 3.93 (0.84-18.44) |
| ∗1/∗2 | Nondrinkers | Ref | Ref |
| | Light drinkers | 15.99 (0.96-266.02) | 13.74 (1.96-96.51)# |
| | Moderate drinkers | 10.95 (1.04-114.88)# | 22.36 (3.69-135.54)# |
| | Excessive drinkers | — | 20.93 (2.77-158.45)# |
| ∗2/∗2 | Nondrinkers | — | — |
| | Light drinkers | — | — |
| | Moderate drinkers | — | — |
| | Excessive drinkers | — | — |

[a]Models were adjusted for age, gender, education, and subtype. *$p < 0.05$ vs. nondrinkers with ALDH2 wild-type genotype (ALDH2 ∗ 1/∗1). #$p < 0.05$ vs. nondrinkers with ALDH2 mutant genotype (ALDH2 ∗ 1/∗2).

elevated following ischemic stroke injury. Guo et al. reported that 4-HNE plays an important role in the pathogenesis of neurological diseases and is a potential biomarker for ischemic stroke [15, 16]. Our data revealed that 4-HNE levels were significantly lower in patients with the *ALDH2* wild-type genotype than in patients carrying mutant *ALDH2* alleles. Meanwhile, patients with the *ALDH2* wild-type genotype were significantly more likely to have a higher MoCA score compared with those carrying mutant alleles. This finding may explain why the *ALDH2* mutant allele carries a significantly higher risk of cognitive impairment.

Swallowing deficits are also commonly reported in patients with ischemic stroke [25]. Several studies revealed that cognitive dysfunction was associated with dysphagia [25, 26]. Therefore, we investigated the association between swallowing function and cognitive impairment using two MoCA cutoff scores. In this study, the severity of dysphagia might contribute to cognitive impairment for both MoCA cutoff scores. In addition, considering that the lesion site may affect the swallowing function, we further adopted subtypes of ischemic stroke to investigate the interaction of ALDH2 and alcohol consumption on swallowing. Our data described that both *ALDH2* genotypes showed a higher risk of dysphagia in excessive drinkers compared to nondrinkers, but the risk of dysphagia was higher in carriers of the mutant *ALDH2* allele than in noncarriers.

As an important determinant of drinking behavior, ALDH2 has a well-known role in ethanol metabolism [47]. Various longitudinal studies have reported a link between moderate alcohol consumption and improved cognitive performance [48, 49]. In our study, we also explored the association between alcohol consumption and cognitive function in patients with ischemic stroke. Considerable evidence has emerged suggesting that alcohol consumption behaviors are related to the *ALDH2 ∗ 2* polymorphism in Asian populations [50, 51]. We divided the ischemic stroke patients in our study into four subgroups based on their history of alcohol consumption. Alcohol consumption in the *ALDH2* wild-type genotype group was significantly higher than that in the mutant and heterozygous genotype group. This may be because carriers of *ALDH2* mutant alleles are more sensitive to alcohol, which reportedly makes them less inclined to engage in excessive drinking [52]. We used two different cognitive impairment cutoff points to analyze the association between alcohol consumption and cognitive impairment. The univariate analysis revealed a higher percentage of moderate to excessive alcohol consumption in the cognitive impairment group than in the nonimpairment group, which suggests that alcohol consumption may have an effect on cognitive impairment after ischemic stroke. We also applied a binary logistic regression model to evaluate the synergistic effects of *ALDH2* polymorphisms and alcohol consumption on cognitive impairment. Adjusted for age, gender, education, and subtype, we demonstrated that the multivariate risk of cognitive impairment was higher in excessive drinkers than in nondrinkers with the *ALDH2* wild-type genotype, while the risk of cognitive impairment was higher in light to excessive drinkers than nondrinkers with the *ALDH2* mutant or heterozygous genotype. These findings further suggest that ALDH2 might be involved in the pathogenesis and progression of cognitive impairment after ischemic stroke, as well as having a role in alcohol metabolism.

There were several limitations in the present study. First, some participants refused to participate, while blood samples were unable to be obtained from some patients; this may have caused sampling bias. Second, the MoCA scale is commonly used as a screening scale for cognitive function but fails to assess global disability after ischemic stroke. So, in this study, we also evaluated the swallowing function. The current findings are therefore considered preliminary and require validation. Third, the plasma 4-HNE levels were detected only once, at baseline, and potential fluctuations in plasma 4-HNE levels were not evaluated; we were therefore unable to adjust for this effect. Finally, although the *ALHD2 ∗ 2* allele

is an important risk factor for ischemic stroke, results have been inconsistent over different ethnic groups, different countries, and different genders. Because the sample size was relatively small, we did not perform a stratified analysis by lesion location. We adopted subtypes of ischemic stroke to replace lesion location, and this might have affected our study results (Supplementary Table 3). To better understand the relationship between ischemic stroke impairment and *ALDH2* genotypes, future studies need to enroll larger sample sizes across multiple communities. To this end, the current study represents an ongoing effort, and we will continue to regularly update the analysis, with the aim of providing a comprehensive and easily accessible review, as well as facilitating a best-practice approach to ischemic stroke rehabilitation.

## 5. Conclusions

The present study demonstrated that *ALDH2* polymorphisms and alcohol consumption were associated with cognitive impairment and dysphagia in patients after ischemic stroke, mainly in patients with the mutant allele. ALDH2 may be involved in the pathogenesis and progression of ischemic stroke in the Han Chinese population. ALDH2 might therefore be a useful biomarker to target for cognitive rehabilitation following ischemic stroke. However, the underlying mechanisms need to be further explored.

## Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethical Approval

This study was conducted with approval from the Ethics Committee of Bengbu Medical College.

## Disclosure

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

## Acknowledgments

This work was supported by the Centers for Disease Control and Prevention of Bengbu, China. The work was also supported by the Natural Science Foundation of the Education Department of Anhui Province (KJ2019A0306), the Transformation of Medicine Research Projects of Bengbu Medical College (BYTM2019004), the 512 Talent Cultivation Plan of Bengbu Medical College (by51201202 and by51201307), and the Chronic Noncommunicable Disease Prevention and Control Program of Bengbu Medical College (BYKC201901), China. We are grateful to all of the professionals and participants involved in the study. We also thank Bronwen Gardner, PhD, from Liwen Bianji, Edanz Editing China (http://www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

## Supplementary Materials

Supplementary Table 1: comparison of MoCA subscores based on ALDH2 polymorphisms and alcohol consumption. Supplementary Table 2: comparison of MoCA subscores based on ALDH2 polymorphisms and alcohol consumption. Supplementary Table 3: multivariate odds ratios (95% confidence intervals) for alcohol consumption on swallowing ability in stroke patients, stratified by ALDH2 polymorphism. *(Supplementary Materials)*

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