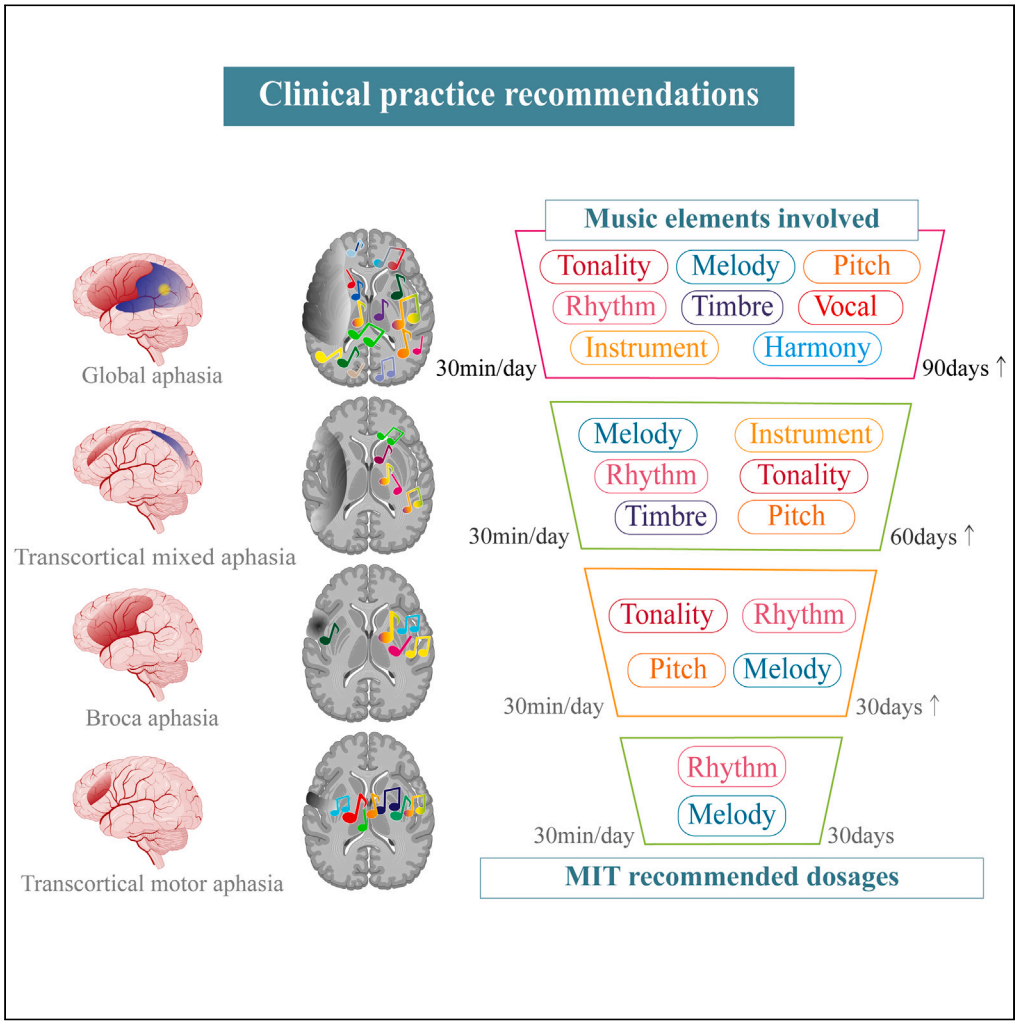
iScience

CellPress
OPEN ACCESS

Article

Melodic intonation therapy for non-fluent aphasia after stroke: A clinical pilot study on behavioral and DTI findings



Xiaoying Zhang, Zuliyaer Talifu, Jianjun Li, Xiaobing Li, Feng Yu

crrclijj@163.com (J.L.)
lxiaobing@ccom.edu.cn (X.L.)
yufengai@ccom.edu.cn (F.Y.)

Highlights

Musical melodic intonation therapy has richer whole-brain effects than traditional ST

MIT showed better behavioral effectiveness than ST

MIT showed richer brain arcuate fasciculus in fMRI-DTI than ST

This study proposed the clinical guidance of MIT intervention

Zhang et al., iScience 26, 107453
September 15, 2023
https://doi.org/10.1016/j.isci.2023.107453

iScience

CellPress
OPEN ACCESS

Article

Melodic intonation therapy for non-fluent aphasia after stroke: A clinical pilot study on behavioral and DTI findings

Xiaoying Zhang,[1,2,3,4,5] Zuliyaer Talifu,[1,4,5] Jianjun Li,[1,4,5,6,7,*] Xiaobing Li,[2,3,6,*] and Feng Yu[2,3,6,*]

SUMMARY

Music-based melodic intonation therapy (MIT) has shown promise as a treatment for non-fluent aphasia after stroke. This trial compared the efficacy of music-based MIT and speech therapy (ST) in aphasia, focusing on arcuate fasciculus connectivity in brain structural and language ability scores. A total of 62 patients were enrolled, of whom 40 completed the trial. The experimental group received MIT for 30 min/d, five days per week for four weeks, while the control group received ST with the same dose. The BDAE and fMRI-DTI were performed at T0 and T1. The music-based MIT group demonstrated better language levels. DTI showed that FA, FN, and path length of the MIT group in the right hemisphere were significantly increased. Music-based MIT had positive effects on reorganization and activation of arcuate fasciculus in aphasia after stroke. This research is funded by NSFC No. T2341003 and No.2020CZ-10. Clinical Trials ChiCTR2000037871. Ethics approval number: 2020-013-1.

INTRODUCTION

Aphasia is an acquired language dysfunction due to organic brain damage to brain regions related to language, causing (partial) impairment in the ability to understand and form language.[1] According to the 2023 Lancet report on the Global Burden of Stroke Risk in countries and regions, the incidence of stroke has increased by 70% worldwide since 1999; there was a prevalence of 85%; and death caused by stroke increased by 43%.[2] Stroke can lead to a variety of functional disabilities, and aphasia is one of the most common complications. About 38% of stroke patients have aphasia symptoms of varying degrees,[3,4] which has a serious effect on quality of life. Due to the irreversibility of nerve damage and language processing disorders caused by structural brain damage, the recovery rate of aphasia is less than 1%,[5] and it is difficult for most patients to recover to their language ability before disease onset.

According to the language fluency of patients, aphasia can be divided into fluent and non-fluent aphasia. Non-fluent aphasia results mainly from damage to the left hemisphere of the brain, presenting difficulties in oral expression; understanding is relatively good, but difficult in terms of word grammar, word order, and sentence delivery. There are different degrees of impairment in naming, reading, and writing.[6] According to the Western classification of aphasia, non-fluent aphasia can be divided into expressive, global, transcortical motor, transcortical sensory, transcortical mixed, conduction, and named aphasia, among others.[7]

Melodic intonation therapy (MIT) is a speech and language generation treatment for patients with severe non-fluent aphasia, which uses melodic intonation, rhythm, tones, and pitch to rehabilitate language function.[8] In 1970, it was officially recognized by the American Association of Neurology as an effective therapy for non-fluent aphasia.[9] MIT is a step-by-step treatment method. It adopts the singing mode of a formulaic melody composed of fixed pitch, intensifies the singing output, or chant pronunciation in the three levels of speech rehabilitation, and verbally outputs the language to be spoken in the form of "singing". Then, under the guidance of a music therapist, the aphasia patient gradually breaks away from the melody and rhythm and speaks at a normal speed.[10]

In recent years, behavioral research and functional magnetic resonance imaging (fMRI) observations from MIT in aphasia have gradually attracted more attention. After a comprehensive inquiry of randomized controlled studies on MIT, compared with traditional speech therapy (ST), MIT improved retelling, daily communication, noun naming, and spontaneous speech ability.[9,11–26] In studies using fMRI, patients treated with MIT activated the auditory center in the undamaged right hemisphere, which corresponds to music processing.[27–30] Via the conduction through the right arcuate fasciculus, MIT activates the right hemisphere speech output region relative to the left hemisphere region, guiding speech production.[26] In case reports of before and after PET test, it was found that patients treated with singing MIT exhibited intact

[1]School of Rehabilitation Medicine, Capital Medical University, Beijing 100068, China
[2]Department of Music Artificial Intelligence and Music Information Technology, Central Conservatory of Music, Beijing 100038, China
[3]Institute of Advanced Science and Technology, Xi'an Jiaotong University, Xi'an 710079, Shanxi, China
[4]Music Therapy Center, China Rehabilitation Research Center, Beijing 100068, China
[5]Department of Neurorehabilitation, China Rehabilitation Research Center, Beijing 100068, China
[6]These authors contributed equally
[7]Lead contact
*Correspondence: crrclijj@163.com (J.L.), lxiaobing@ccom.edu.cn (X.L.), yufengai@ccom.edu.cn (F.Y.)
https://doi.org/10.1016/j.isci.2023.107453

right basal ganglia and left temporal lobes.[35,36] In the MIT case report using MEG, the patient improved in language function to MIT, and exhibited a steady reduction in activation within the right hemisphere across the two therapy blocks, resulting in a strong left hemisphere lateralization of MEG activity.[20] In self-controlled studies using SPECT, the patient showed a totally uniform pattern in the relative perfusion changes. The pattern indicated increased right hemisphere during MIT.[37]

Diffusion tensor imaging (DTI) is an innovative method for observing the structure of the brain, a particular type of magnetic resonance imaging (MRI).[31] DTI mainly tracks the movement of water molecules in nerve fibers to build a connected graph among brain regions and reconstruct brain networks. MIT activates the right-brain language–motor regions corresponding to the left-brain Broca's area through the right hemisphere arcuate tract; this is a type of compensation and induces speech output.[26] However, most studies focused on case reports or were self-controlled with fewer than 10 cases, and there are no observational studies using DTI with larger sample sizes. In the present clinical trial, the standard melodic articulation therapy method was used to compare the effectiveness of ST and MIT in non-fluent aphasia using the Boston Diagnostic Aphasia Examination (BDAE) scale and 3.0T fMRI-DTI imaging.

Methods

Study design

This pilot clinical trial used a before-and-after test design including two groups—an experimental group (n = 20) and a control group (n = 20). The study was an open-label pilot study; participants knew they were engaging in a clinical trial and the grouping. The formula $n = Z2 \cdot \sigma 2/d2$ is calculated according to the sample size. Z is the confidence interval, taking the value of 90%. Σ is the standard error; D is the error range (0.15), and the minimum sample size n = 31 is obtained. Therefore, this pilot study meets the requirement of minimum sample size. Computer-generated sequences were used (Excel 2013, USA, WA, Seattle, Microsoft Office) to divide into two groups. An anonymous data analyst did not know which dataset was being tested and analyzed. ST was given to the control group while MIT was given to the experimental group. From April 2020 to November 2022, the study was conducted at the China Rehabilitation Research Center (CRRC) China. This work was supported by the Special Fund for Basic Scientific Research of Central Public Research Institutes of the Chinese Institute of Rehabilitation Sciences, "Clinical and mechanism study of MIT for non-fluent aphasia after stroke" (grant number 2020CZ-10), and the National Natural Science Foundation of China Special research project "Music Intelligence Quantification and Brain Science Cognition Research" (No. T2341003). The research protocol was approved by the Ethics Committee of the CRRC (Approval number: 2020-013-1; April 1, 2020; Document S1), and participants or their families provided written informed consent (Document S2) before commencing the study. The trial was registered with the Clinical Trial Registry (Registration No. ChiCTR2000037871) on September 3rd, 2020.

Participants

Sixty-two patients with stroke hospitalized in Beijing Bo'ai Hospital, China Rehabilitation Research Center, were selected. The inclusion criteria were: (1) left hemisphere ischemic stroke or hemorrhagic stroke diagnosed by fMRI or computed tomography (CT); (2) the 9th speech score on the National Institutes of Health Stroke Scale (NIHSS)[27] was 1 (mild/moderate aphasia) or 2 (global aphasia); (3) patients with non-fluent aphasia assessed by the BDAE as expressive aphasia, complete aphasia, transcortical motor aphasia, or transcortical mixed aphasia; (4) according to the diagnostic criteria for non-fluent aphasia, patients had the willingness to actively express, poor speech expression, some listening and comprehension ability, could decide whether or not to respond, cooperated with rehabilitative therapy, and were emotionally stable;[14] (5) inpatients with aphasia for more than 0.5 months after stroke, that is, patients with non-fluent aphasia in the recovery period after stroke; (6) 18–80 years old; (7) could perform training for more than 30 min without rest; (8) Other neurotrophic medication are consistent; (9) patients received the same types of other physical therapy and standard care; (10) no previous professional music education experience; (11) participants and their guardians provided written informed consent (Document S2).

The exclusion criteria were: (1) severe hearing impairment; (2) epilepsy, arrhythmia, sitting hypotension, or other serious diseases; (3) severe psychiatric symptoms or serious behavioral agitation.

Termination of study participation was possible if a patient's circumstances changed, if they were discharged, or they voluntarily withdrew. There were 62 patients involved in this clinical trial, and 40 participants completed the trial. Twenty-two participants withdrew from the trial; 13 withdrew because of the COVID-19 pandemic, 6 because of intermediate referrals, and 3 because of personal reasons.

Patient recruitment was conducted from January 2020 to December 2022. Table 1 shows the characteristics of participants. Sixteen participants (80%) in the MIT intervention group were men, and seventeen (85%) in the ST intervention group were men. Participants in the experimental (MIT) group were, on average, 50.15 years old (SD 15.44), and control group participants (ST) were, on average, 51.6 years (SD 14.27). Eleven participants (55%) in the experimental group had a diagnosis of ischemic stroke and 9 (45%) were diagnosed with hemorrhagic stroke; the mean time since injury was 2.3 months (SD 1.29); eight control participants (40%) were diagnosed with ischemic stroke and 12 (60%) with hemorrhagic stroke, and the mean time since injury was 1.8 months (SD 1.39). Nine (45%) participants in the MIT group were diagnosed with complete aphasia, four (20%) with Broca's aphasia, three (15%) with transcortical mixed aphasia, and four (20%) with transcortical motor aphasia. Seven control participants (35%) were diagnosed with global aphasia, three (15%) with Broca's aphasia, two (10%) with transcortical mixed aphasia, and eight (40%) with transcortical motor aphasia.

Procedure

After approval by the Ethics Committee and the Foundation for Scientific Research, participants were first screened by neurorehabilitation physicians. Patients diagnosed with mild-to-moderate aphasia and severe aphasia on the 9th language score of the NIHSS were referred

Table 1. Participant baseline characteristics

	Melodic Intonation Therapy (n = 20)	Speech therapy Group (n = 20)	p
Gender			
Male	16(80%)	17(85%)	
Female	4(20%)	3(15%)	1
Age			
Mean (SD)	50.15(15.44)	51.6(14.27%)	
Median (IOR)	54.0(28.25)	50.5(14.75)	0.7666
Range	18–74	18–80	
Diagnosis			
Ischemic stroke	11(55%)	8(40%)	
Hemorrhagic stroke	9(45%)	12(60%)	0.5273
Time post-injury			
Months (SD)	2.313(1.29)	1.819(1.39)	0.1295
Aphasia type (T1)			
Global aphasia	9(45%)	7(35%)	
Broca's aphasia	8(40%)	11(55%)	
Transcortical mixed aphasia	3(15%)	2(10%)	0.5962
Transcortical motor aphasia	4(20%)	8(40%)	

Data included gender, time of injury, stroke type, and classification of non-fluent aphasia. A paired t-test was performed on other data, expressed as mean (SD), between MIT and ST groups. p-values < 0.005 indicated statistical significance.

to the departments of speech and of music therapy. Participants were initially assessed and identified for inclusion. When a participant met the inclusion criteria, the researchers invited the participant's family members to participate in the informed consent interview. This included explaining to the patient and their family what the study was about, what it entailed, the risks, the benefits, and what the participants' rights were. Once the participant and their family members provided written informed consent, participants were evaluated by a professional evaluator for BDAE[28] to determine the type of non-fluent aphasia. The participants were then scheduled for pre-intervention fMRI-DTI examination. The researchers began assigning patients based on the BDAE score, using a computer-generated sequence (Excel 2013, Microsoft Office, Seattle, WA, USA) to randomly assign patients to two groups. The experimental group received MIT from a registered music therapist for 4 weeks, while the control group received ST from a speech therapist for 4 weeks. The registration and assignment of participants are shown in Figure 1.

Interventions. For both MIT and ST, each patient trained for 30 min at a session, five sessions per week. To ensure the quality of the training process, MIT therapists were trained in neurological music therapy (NMT) and licensed as registered music therapists. ST professionals who were licensed as rehabilitation therapists conducted the ST training process.

Music-based melodic intonation therapy. The steps of the MIT intervention were strictly based on the Mandarin MIT, and the training content was divided into 1–15 character sentences according to the three levels of language rehabilitation.[10] The training method was the formulaic melodic language of fixed-pitch melody.[26] The principle of this is to simulate formulaic short melodies for patients to sing according to the natural pitch of the language of daily life dialogue.[10,26] MIT uses very strict procedures, including the original Norton (2009) published 6-step method (including tapping, arrow to indicate the direction of intonation, a steady rhythm) until later modified MIT derived from different languages in different countries. But, unfortunately, Norton[12] did not elucidate the fixed pitch. Therefore, the use of the composed fixed pitch as the short melody of MIT intervention is an important intervention feature of the Chinese version of MIT. According to the characteristics of Chinese aphasia, the steps of MIT based on music therapy are successively: (1) monophonic recording of the target vocabulary, (2) monophonic singing, (3) chord accompaniment singing, (4) chord singing fading, (5) accompaniment joint rhythm singing, (6) rhythm singing fading, (7) repetition, (8) delayed repetition, (9) normalization, (10) episodic dialogue (Document S3, MIT music scores).[26] After several MIT sessions, patients completely learned and then separated the language from the musical tones in the form of questions and answers for the patient to speak. In MIT, a music therapist uses an instrument such as a keyboard or guitar to provide harmonic support when leading the patient to sing the formulaic melodic language, until the patient is fully familiar with the formulaic melodic language and can answer questions in verbal form (Document S4, MIT Video) intervention dose was 30 min each session, five days a week for four weeks.

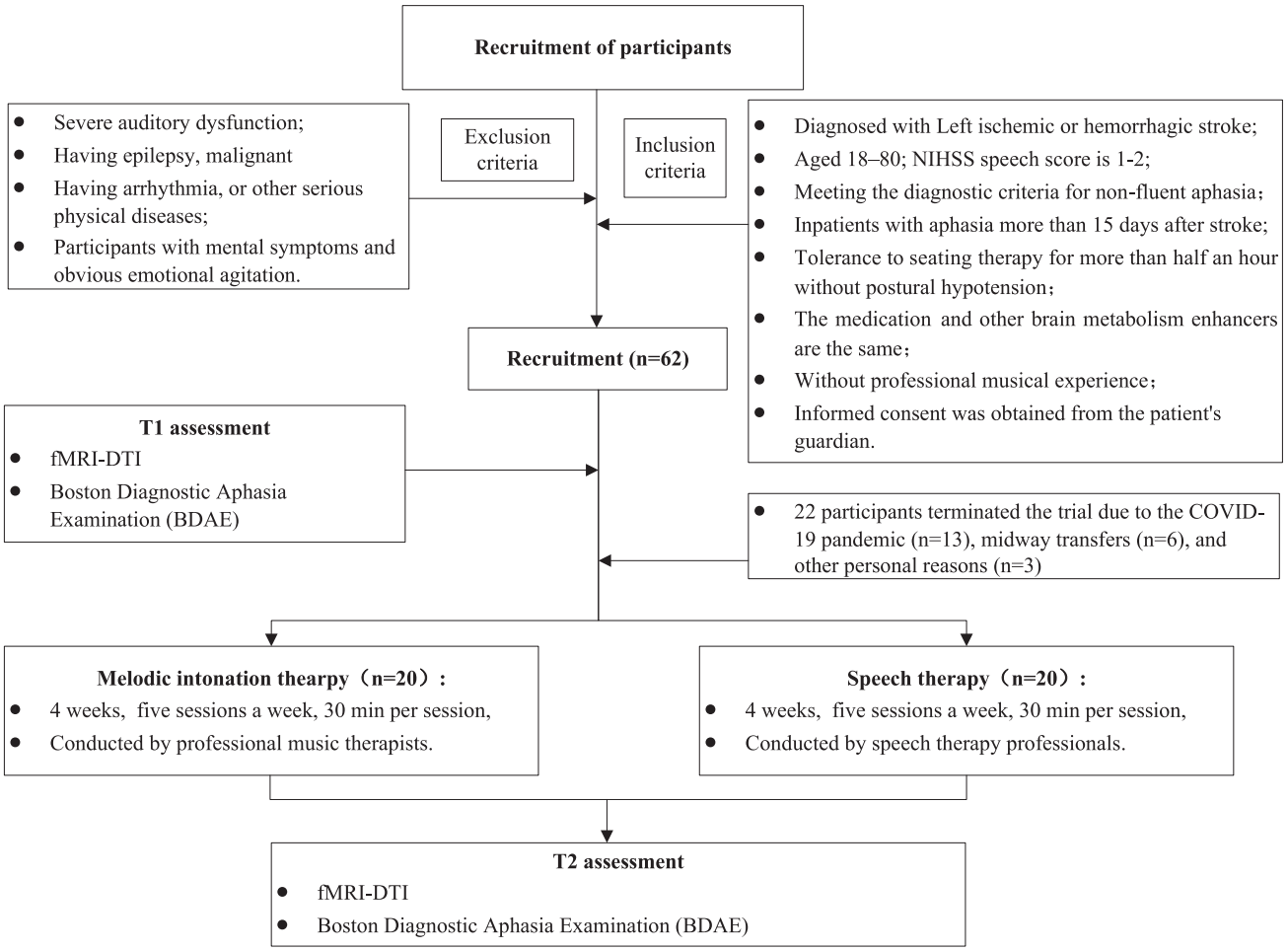


Figure 1. An overview of the recruitment and allocation process for participants, a flow diagram for the consortium

The study enrolled 62 participants, but 22 withdrew for various reasons; the COVID-19 pandemic (13 participants), midway transfers (6 participants), or other personal reasons (3 participants); There was an experimental group of 20 treated with melodic intonation therapy by registered music therapists and a control group of 20 treated with speech therapy by speech therapists; There were two evaluations conducted during the study, one at T0 (baseline), the other at T1 (after 4 weeks); The sample for the data analysis was 40 patients with non-fluent aphasia.

Speech therapy. In the ST group, patients were trained using picture recognition; perception exercises, for example, to differentiate between individual sounds and syllables; producing certain sounds; word imitation; and mouth imitation to improve the fluency of speech. Training was also conducted five times a week for four weeks for 30 min each session.

In both experimental and control groups, 16 cases of global aphasia (n = 9, n = 7), seven cases of Broca's aphasia (n = 4, n = 3), five cases of transcortical mixed aphasia (n = 3, n = 2), and 12 cases of transcortical motor aphasia were reported (n = 4, n = 8).

Measurements. Prior to the initiation of treatment, participants were assessed at baseline by a professional evaluator using (1) the BDAE[28] and (2) DTI.[30] A second BDAE and DTI test were performed after 4 weeks of therapy to observe behavioral and imaging changes. No participants had an open tracheostomy, ambulatory blood pressure monitoring, or difficulty breathing at the time of the evaluation.

Boston Diagnostic Aphasia Examination. In the BDAE, language skills are assessed based on perceptual patterns (auditory, visual, gestural), processes (understanding, analysis, problem-solving), and responses (writing, pronunciation).[26] In most cases, the BDAE takes 30 min. It is a recognized universal language assessment scale that can be used in multiple languages and has high reliability and validity. It includes not only the examination of language function itself but also the examination of non-verbal function, which can be used for quantitative analysis of the predictive communication level of patients. Additionally, it can be used to determine the severity of aphasia, and it can be used to classify patients who have aphasia.

The BDAE consists of 27 sub-tests, including dialogue and spontaneous speech, listening comprehension, speech expression, written comprehension, retelling, and naming, among others. Based on the formula for calculating the Aphasia Quotient (AQ), the above subtests

are combined to produce the total score. Thus, this approach provides a comprehensive treatment that matches language-related skills and abilities with pathological conditions.[30]

Diffusion tensor imaging. Brain structure can be determined using fMRI-DTI, a special form of MRI.[29] Water molecules in the brain are tracked by DTI to create maps of the connections between cells and to reconstruct the brain's network structure. This study focused on three observations from DTI: (1) fractional anisotropy (FA), which is the degree to which water molecules are displaced spatially in nerve fiber tracts and is related to the elongation direction of white matter fibers,; (2) fiber number (FN), which is the density of nerve fiber tracing; and (3) path length (Length), which mainly refers to the optimal path for a node to reach another node in the brain network.

Single-shot echo-planar pulse sequences were used to acquire DTI data. A 3.0-T MRI scanner (Philips Ingenia, Best, Netherlands) with an 8-channel phase-array head coil was used to obtain MRI images of the patient in a supine position. Earplugs were provided to reduce scanning noise, and tight but comfortable foam padding was used to minimize head movements. Three-dimensional (3D) structural T1-weighted images were obtained with the following parameters: repetition time (TR)/echo time (TE) = 7.0/3.2 ms; flip angle = 7°; 192 slices; 1-mm slice thickness; field of view = 256 × 256 mm^2, matrix = 256 × 256, isotropic resolution of 1 mm^3. We obtained resting-state functional data using any combination of echo-planer imaging and the following parameters: TR, 2000 ms; TE, 30 ms; slice thickness, 3.5 mm; number of slices, 32; FOV, 224 × 224 mm; matrix size, 64 × 64; interslice gap, 0.8 mm; flip angle, 90°. One image with b = 0 s/mm^2, 32 independent directions, b = 1000 s, thickness = 2 mm, TR = 10624 ms, TE = 89 ms, flip angle = 90°, slice gap = 0, FOV = 224 × 224 mm, matrix size = 1.

Statistical analysis

The data were analyzed using SPSS 23.0[26] for comparisons between pre- and post-treatment. A paired t-test was used if data were normally distributed and the variance was homogeneous; p value correction was used if data were normally distributed and the variance was not homogeneous; and Wilcoxon signed-rank test was used if data were not normally distributed. For comparisons between the two groups, independent-samples t-tests were performed if the data were normally distributed and the variance was homogeneous; for normally distributed data with non-homogeneous variance, p-value-correction was used; if the data were not normally distributed, the U test was used to calculate the statistical value. p-values <0.05 were considered statistically significant.

RESULTS

Both MIT and ST significantly improved speech function in patients with non-fluent aphasia

The severity of aphasia was assessed by using the BDAE scale in five areas: AQ, Spontaneous speech, listening comprehension, repetition, and naming. After a 4-week treatment period, the BDAE scale scores of the participants in the MIT and ST groups showed a significant increase in the speech level (except for spontaneous speech; fluency T0 vs. T1 p = 0.0225 in the ST group; all T0 vs..T1 p values were <0.01), as shown in the Table 2.

Specifically, the AQ scores improved in the MIT group (p = 0.0001; Figure 2A). Spontaneous speech information score is improved in the MIT group (p = 0.0001; Figure 2B). Spontaneous speech Information scores in the MIT group is increased (p = 0.0001; Figure 2C). Spontaneous speech Fluency score is increased (p = 0.0001; Figure 2D). Listening comprehension quotient scores increased in the MIT group (p = 0.0012; Figure 2E). Listening comprehension words increased in the MIT group (p = 0.0001; Figure 2F). MIT group Listening comprehension-True of False scores increased (p = 0.0001; Figure 2G). Listening comprehension sequential commands scores improved (p = 0.0001; Figure 2H) in the MIT group.

Partial BDAE item scores were significantly in the MIT group

All data from the MIT and ST groups at the T0 assessment showed no differences (all p values >0.05; Table 3). However, after 4 weeks of therapeutic interventions, the MIT group demonstrated better spontaneous language levels (p = 0.0037; Figure 2B), better spontaneous language information (p = 0.0014, Figure 2D), and better sentence completion ability (p = 0.0359, Figure 3E).

Repetition scores were increased in the MIT group (p = 0.0001; Figure 3A). The naming quotient scores increased (p = 0.0001, Figure 3B) in the MIT group. Object naming scores in the MIT group improved from 14.95 ± 17.44 to 30.9 ± 18.22 (p = 0.0001), and the ST group improved from 17.95 ± 21.81 to 27.55 ± 20.8 (p = 0.0001; Figure 3C). The reaction naming scores increased from 2.4 ± 3.26 to 6 ± 3.29 in the MIT group (p < 0.0001) and from 3.15 ± 4.04 to 6.3 ± 3.86 in the ST group (p = 0.0001; Figure 3D). Sentence completion scores improved in the MIT group (p = 0.0116; Figure 3E). Spontaneous naming scores improved in the MIT group (p = 0.0001; Figure 3F).

At the T0 assessment, all data from the MIT and ST groups showed no difference (all p values >0.05), while the MIT group demonstrated better spontaneous speech levels (MIT vs. ST, p = 0.0037) and better spontaneous speech information (MIT vs. ST, p = 0.0037) and sentence completion ability (MIT vs. ST, p = 0.0359) than the ST group after 4 weeks of therapeutic intervention.

Visualization of MIT effects on neural plasticity of cerebral networks in patients with non-fluent aphasia after stroke

After the TrakVis: Diffusion Toolkit analysis using MATLAB software (The MathWorks, Natick, MA, USA), in the newly determined fine distribution of 246 Brainnetome Atlas regions,[32] the MIT group showed higher FA, FN, and Length. The specific brain regions included the dorsolateral area and the middle area of the right superior frontal gyrus, the ventrolateral area of the right middle frontal gyrus, the caudal area of the inferior frontal gyrus, the medial area of the orbitofrontal cortex, the caudal dorsolateral area of the precentral gyrus, the medial area of

Table 2. The results of BDAE

			T1 Mean ± SD	T2 Mean ± SD	*t/W*	*p*
Aphasia Quotient	(AQ)	MIT	30.77 ± 22.10	53.75 ± 22.31	0	0.0001
		ST	37.69 ± 26.70	46.82 ± 25.73	0	0.0001
Spontaneous speech	Sum	MIT	6.30 ± 3.74	12.30 ± 3.95	0	0.0001
		ST	6.40 ± 4.77	8.15 ± 4.90	6	0.0003
	Information	MIT	3.85 ± 2.06	7.95 ± 3.01	0	0.0001
		ST	3.55 ± 2.69	4.70 ± 2.81	0	0.0001
	Fluency	MIT	2.65 ± 1.74	4.35 ± 1.82	0	0.0001
		ST	2.85 ± 2.17	3.45 ± 2.33	31	0.0225
Listening comprehension	Quotient	MIT	3.55 ± 2.58	4.39 ± 2.62	18	0.0012
		ST	4.87 ± 2.92	5.45 ± 2.87	0	0.0001
	True or False	MIT	29.55 ± 17.37	34.65 ± 17.36	0	0.0001
		ST	35.70 ± 17.62	38.75 ± 17.69	−8.868	<0.0001
	Words recognition	MIT	26.85 ± 18.59	30.05 ± 19.27	20	0.0015
		ST	36.15 ± 18.83	39.45 ± 18.56	0	0.0001
	Sequential commands	MIT	14.55 ± 22.06	23.05 ± 22.87	1	<0.0001
		ST	25.45 ± 27.99	30.70 ± 27.38	−10.4588	<0.0001
Repetition	Quotient	MIT	3.45 ± 3.56	5.44 ± 3.82	0	0.0003
		ST	5.10 ± 4.51	5.69 ± 4.28	0	0.0038
	Repetition	MIT	34.50 ± 35.61	57.21 ± 37.06	0	0.0003
		ST	51.00 ± 45.12	59.89 ± 41.84	0	0.0038
Naming	Quotient	MIT	2.09 ± 2.43	4.75 ± 2.65	0	0.0001
		ST	2.48 ± 3.00	4.13 ± 2.90	−10.5667	<0.0001
	Objective naming	MIT	14.95 ± 17.44	30.9 ± 18.22	0	<0.0001
		ST	17.95 ± 21.81	27.55 ± 20.8	−8.4818	<0.0001
	Spontaneous naming	MIT	1.40 ± 1.93	3.40 ± 3.09	0	0.0003
		ST	1.50 ± 2.75	3.55 ± 2.91	0	0.0001
	Sentences completing	MIT	2.10 ± 3.30	7.20 ± 4.76	0	0.0001
		ST	2.20 ± 3.03	3.85 ± 3.73	−2.7937	0.0116
	Reaction naming	MIT	2.40 ± 3.26	6.00 ± 3.29	0	<0.0001
		ST	3.15 ± 4.04	6.30 ± 3.86	0	0.0001

The results in patients with non-fluent aphasia across the study period for the MIT therapy group and the ST group. Data were expressed as mean ± SD (n = 20), independent samples t-test or Wilcoxon-test. ***P<0.001, **P<0.01, remarkable significance; *P<0.05, significance. Superscript a represents difference factor at the same time between groups, and superscript b represents difference effect of time factor in inter-group.

right superior temporal gyrus, the rostral area of right transverse temporal gyrus, the inferior temporal gyrus, the caudal area of right parahippocampal gyrus, the caudal area of the right inferior parietal lobule, the precuneus, postcentral gyrus, insular gyrus, cingulate gyrus of the limbic lobe, corpus callosum, and subcortical nucleus. In Figures 4, 5, 6, and 7, comparisons of the two groups are shown. In Table 4, the highlighted region of interest shows changes in FA, FN, and Length after music-based MIT intervention.

DISCUSSION

The present study focused on the relationship between music-based MIT-induced changes in brain structural connectivity and speech function scores in patients with non-fluent aphasia after stroke. In the process of MIT treatment, patients with complete aphasia and transcortical mixed aphasia can imitate MIT short melodies, especially melodic intervals within the fifth degree, after receiving music guidance - MIT training. Patients with Broca's area aphasia and transcortical sport aphasia were more effective at mimicking long melodies. This is consistent with the MIT principle of using formulaic short melodies. The results show up in behavioral assessments. Compared with traditional ST, MIT enhanced neural fiber bundles and functional connections. In particular, according to the fine distribution of 246 brain regions newly determined in 2016,[32] remodeling between the superior longitudinal fasciculus and the frontotemporal and inferior parietal lobule in the temporal regions BA41 and BA42 (Brainnetome Atlas A41/42, area 41/42 of STG_L[R]) of the right hemisphere was clearly associated with aphasia

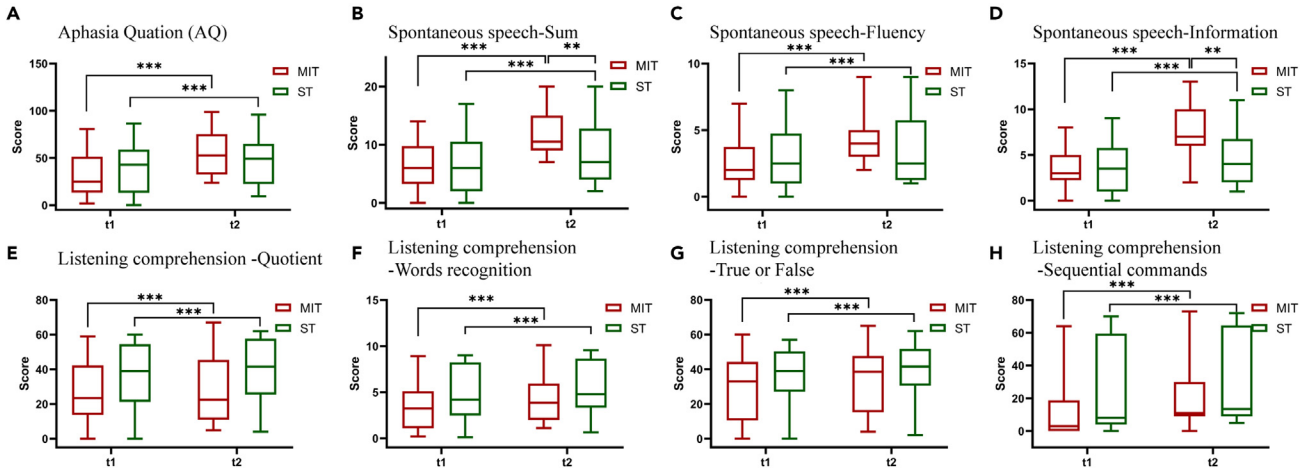


Figure 2. Comparison of results of Boston Diagnosis Aphasia Examination (BDAE) scores in aphasia quotient (AQ), spontaneous speech, and listening comprehension before and after MIT and ST interventions in patients with aphasia

(A–H) (A) AQ, (B) Spontaneous speech sum, (C) spontaneous speech fluency, (D) spontaneous listening comprehension information, (E) listening comprehension quotient, (F) listening comprehension word recognition, (G) listening comprehension true/false (H) listening communication; ***$p < 0.001$,**$p < 0.01$, *$p < 0.05$.

recovery. This was reflected by semantic comprehension (sentence completion), an obvious increase in spontaneous speech, and the enhancement of semantic information. BA40 (A40rv, rostroventral area 40 [PFop]) is connected to the superior temporal gyrus via the arcuate fasciculus, which connects the posterior superior temporal area to dorsolateral frontal areas 7 and 8 and middle areas 9–14 located above areas BA41/BA42 and BA44/BA45. This indicated that MIT based on music activated network connectivity of the right frontal lobe, right precentral gyrus, right temporal lobe, right inferior parietal lobule, right postcentral gyrus, lateral occipital cortex, and subcortical nucleus. There is a positive correlation between spontaneous speech, information amount, and responses. In spontaneous speech, the maximum FA and FN values in the global network were located in the head and face region of the right precentral gyrus; the tongue and larynx region of the right postcentral gyrus; the right frontal lobe; the right temporal lobe; and the right inferior parietal lobule. In the MIT group with repeated speech information training, the maximum values in the global network were more distributed in the superior temporal gyrus, transverse temporal gyrus, and ventral postcentral gyrus. This suggested that the verbal output of repeated formulaic melodic phrases was primarily related to the regions involved in speech production. Short melodies combined with the natural sounds of everyday idioms, through continuous musical input, enabled the network of the right hemisphere of the brain to process pitch information while also generalizing the verbal output mechanisms of speech. On the one hand, this was in line with the basic understanding of the melody-processing mechanisms in the right hemisphere; on the other hand, it also suggested that the perception, recognition, acquisition, and output of pitch require the participation of a wide range of brain networks, mainly in the right hemisphere.

The effects of MIT on fractional anisotropy (FA) in non-fluent aphasia

FA is generally used to quantitatively analyze the direction of white matter fibers in the brain, reflecting the proportion of water molecular anisotropy. In the present study, patients in the MIT group diversified their FA-weighted structural networks. Especially in the right superior frontal gyrus, middle frontal gyrus, anterior central gyrus, most of the temporal lobe, and inferior parietal lobules (Figure 5), the increased number of nodes in these regions suggested that they were more active in the neural network involved in melody imitation singing. In the network nodes, there was an obvious improvement in the superior temporal gyrus, middle temporal gyrus, mediolateral area, lateral area, and ventral inferior temporal gyrus. Activity related to semantic comprehension and verbal output was observed in the rostral and caudal regions of the inferior parietal lobule, in the postcentral gyrus, and in the cingulate gyrus of the limbic lobe (Figure 7). As the speech-motor output was given as a melody, changes in the direction of arcuate fasciculus connections began to follow neuronal signals, thereby driving the direction of water molecules. In the MIT group, high signal intensity was found in the medial lateral area, lateral area, ventral inferior temporal gyrus, and the tail of the parahippocampal gyrus. This indicated that activity in the auditory nerve center, involved in music processing, was increased during singing, and more complex neural activity occurred during speech output than verbal vocabulary processing. Compared with the ST group, the MIT group showed significantly higher signals at the nodes of the functional network matrix with specific signal oscillation frequencies, and the response at the global level of the FA-weighted structural network was higher than the threshold. Therefore, MIT training had a positive effect on the multi-directional alignment and regeneration of FA nerve fiber bundles.

Effects of MIT on FN and length of neural fiber tracts in non-fluent aphasia

In the analysis of FN nodes and length, the regions with enhanced motor activity with melodic verbal output in the FN-weighted structural network were also mainly distributed in the caudal area of the right inferior parietal lobule, precuneus, cingulate gyrus of the limbic lobe,

Table 3. Independent samples t-test between two groups

			MIT Group (n = 20) Mean ± SD	ST Group (n = 20) Mean ± SD	*t/W*	*p*
Aphasia Quotient	(AQ)	t1	30.77 ± 22.10	37.69 ± 26.70	−0.8708	0.3893
		t2	37.69 ± 26.70	46.82 ± 25.73	0.8865	0.3809
Spontaneous speech	Sum	t1	6.30 ± 3.74	6.40 ± 4.77	−0.0719	0.9431
		t2	12.30 ± 3.95	8.15 ± 4.90	307.5	0.0037[b]
	Information	t1	3.85 ± 2.06	3.55 ± 2.69	0.386	0.7016
		t2	7.95 ± 3.01	4.70 ± 2.81	3.4402	0.0014[b]
	Fluency	t1	2.65 ± 1.74	2.85 ± 2.17	195	0.9017
		t2	4.35 ± 1.82	3.45 ± 2.33	256.5	0.1257
Listening comprehension	Quotient	t1	3.55 ± 2.58	4.87 ± 2.92	150	0.1805
		t2	4.39 ± 2.62	5.45 ± 2.87	158	0.2648
	True or False	t1	29.55 ± 17.37	35.7 ± 17.62	160.5	0.2903
		t2	34.65 ± 17.36	38.75 ± 17.69	175	0.5073
	Words recognition	t1	26.85 ± 18.59	36.15 ± 18.83	−1.5318	0.1339
		t2	30.05 ± 19.27	39.45 ± 18.56	141.5	0.1165
	Sequential commands	t1	14.55 ± 22.06	25.45 ± 27.99	137	0.085
		t2	23.05 ± 22.87	30.70 ± 27.38	178.5	0.5667
Repetition		t1	34.50 ± 35.61	51.00 ± 45.12	165.5	0.3427
		t2	54.35 ± 38.21	59.89 ± 41.84	163.5	0.6263
Naming	Quotient	t1	2.09 ± 2.43	2.48 ± 3.00	207.5	0.8472
		t2	4.75 ± 2.65	4.13 ± 2.90	248	0.1986
	Objective naming	t1	14.95 ± 17.44	17.95 ± 21.81	208	0.8357
		t2	30.90 ± 18.22	27.55 ± 20.8	249	0.1888
	Spontaneous naming	t1	1.40 ± 1.93	1.50 ± 2.75	211.5	0.7264
		t2	3.40 ± 3.09	3.55 ± 2.91	184.5	0.6782
	Sentences completing	t1	2.10 ± 3.30	2.20 ± 3.03	190	0.7746
		t2	7.20 ± 4.76	3.85 ± 3.73	277.5	0.0359[a]
	Reaction naming	t1	2.40 ± 3.26	3.15 ± 4.04	177.5	0.5135
		t2	6.00 ± 3.29	6.30 ± 3.86	181.5	0.6195

The BDAE results in patients with non-fluent aphasia across the study period for the MIT and ST groups; In addition to the means and SDs (n = 20), data were analyzed using independent samples t-tests or U tests.

During the same time period, superscript a represents the difference factor between groups, while superscript b represents the intergroup effect of the time factor.

[a]$p < 0.05$.

[b]$p < 0.01$.

and corpus callosum (Figure 4). The tongue and laryngeal regions located in the inferior parietal lobule, which are related to speech movements, also showed corresponding increased motor activity. This was inseparable from the patient's daily quantitative singing activity because singing involves multiple levels of spoken language execution, such as verbal word movements. This had a positive effect on the experimental participant group.

Regarding brain network path optimization, the effects of singing on the length of nerve fiber tracts was higher than that on FN. Specifically, after music-based melodic articulation therapy, patients in the MIT group showed an increase in the length of nerve fiber tracts from the frontal lobe to the parietal lobe, temporal lobe, corpus callosum, thalamus, hippocampus, insula, cingulate, and back to the subcortical nucleus. The extended network effects in the arcuate fasciculus in the MIT group were significantly greater than those in the ST group. The information exchange level of the nodes of the FN- and length-weighted structural network was significantly higher in the MIT group, and the distribution characteristics of the nerve fiber tracts were the same as those for the FA (Figure 6). The increase in the number and length of fiber tracts accelerates the overall efficiency of neural signal processing. The growth of the FA with length was observed throughout the telencephalon, midbrain, corpus callosum, pons, and medulla oblongata. This suggests that singing-based MIT globally activated music processing networks, promoting both functional and structural brain reorganization. In MIT, "singing" words used in everyday life is a key component.

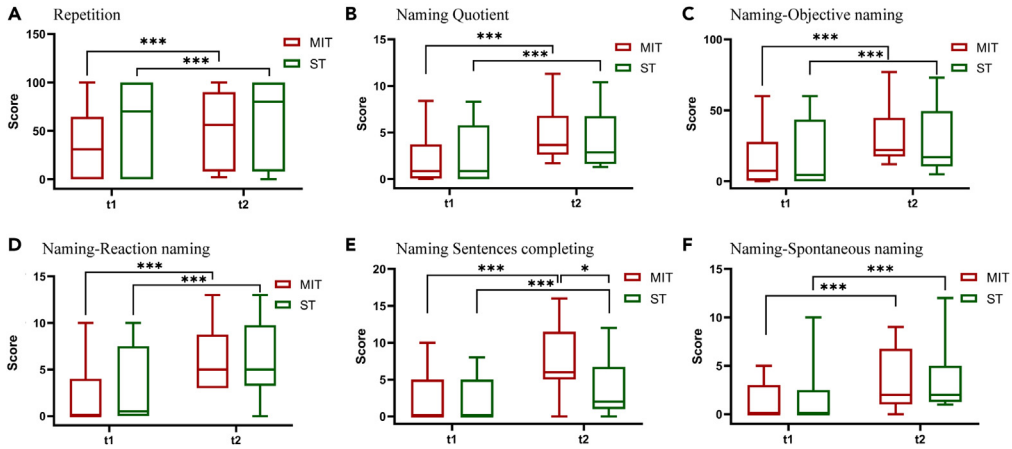


Figure 3. Comparison of the results of the Boston Diagnosis Aphasia Examination (BDAE) in Repetition; naming before and after MIT and ST interventions in patients with aphasia

(A–F) (A) repetition, (B) naming quotient, (C) object naming, (D) naming-reaction naming, (E) naming sentence completion, (F) naming-spontaneous naming; ***p < 0.001,**p < 0.01, *p < 0.05.

Bilateral output involving frontotemporal language and voice motor areas, as well as temporal lobe activity involved in auditory nerve signal processing, is more extensive than the networks activated by speech alone.[22,33] Together with neural processing in the parietal and subcortical areas related to oral, tongue, and laryngeal sensorimotor functions and head and face movements, this increases the output efficiency of spoken language. Thus, singing enables patients with non-fluent aphasia to perform simultaneous language training through areas preserved in the left hemisphere and intact functional areas in the right hemisphere, greatly improving the efficiency of aphasia rehabilitation.

Effects of core factors of music on functional plasticity in MIT

The core factor of MIT is musicalization. Whether this is the variety of instruments used by music therapists, the capture of pitch sensitivity, or the level of vocal music, these all influence the implementation of MIT. For patients with non-fluent aphasia, the more musical formulaic

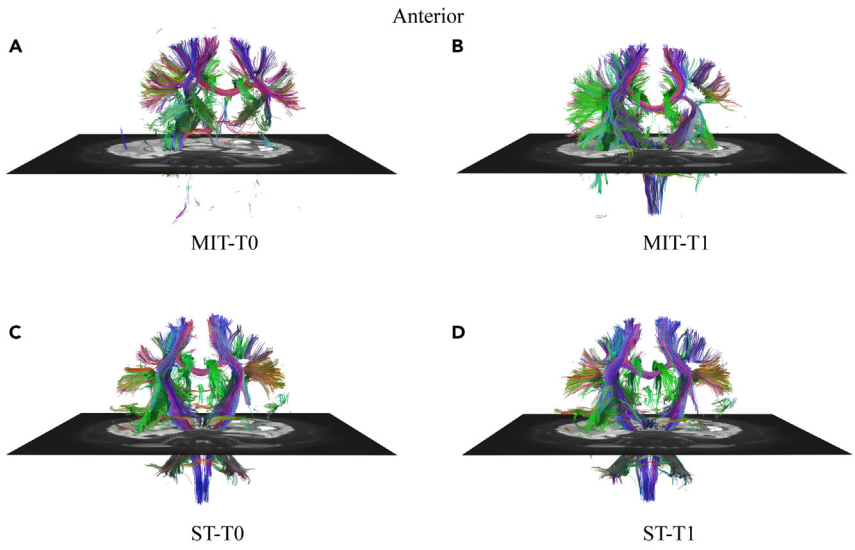


Figure 4. Comparison of neural plasticity of cerebral networks based on DTI 3D visible images in the anterior plane in patients with non-fluent aphasia after stroke in two groups

(A–D) Anterior, anterior plane; MIT, melodic intonation therapy group (experimental group); ST, speech therapy group (control group); T0, baseline time point, before intervention; T1, after one month of intervention; (A) MIT-T0, melodic intonation therapy group (experimental group) on baseline time point; (B) MIT-T1, melodic intonation therapy (experimental group) after one month (C) ST-T0, speech therapy group (control group) at baseline time point; (D) ST-T1, speech therapy (control group) after one month.

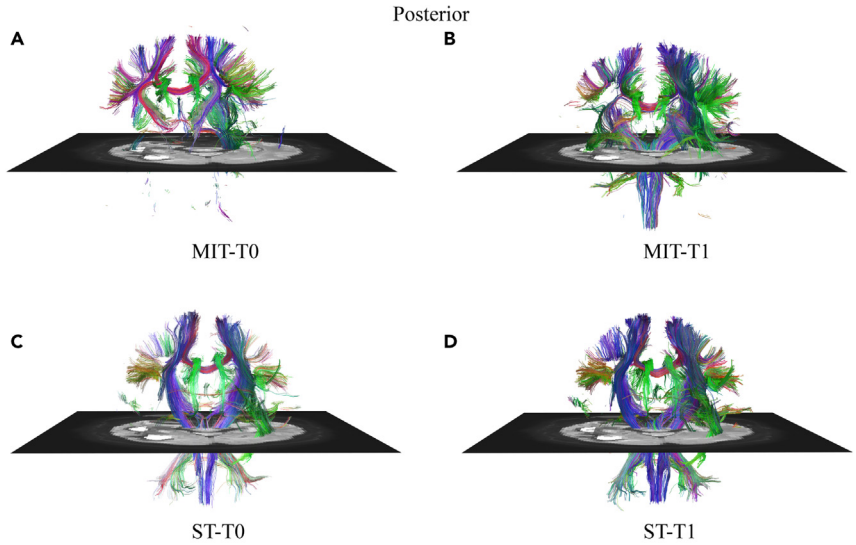


Figure 5. Comparison of neural plasticity of cerebral networks based on DTI 3D visible images in the posterior plane in patients with non-fluent aphasia after stroke in two groups; posterior, posterior plane

MIT, melodic intonation therapy group (experimental group); ST, speech therapy group (control group); T0, baseline time point, before intervention; T1, after one month of intervention.

(A) MIT-T0, melodic intonation therapy group (experimental group) on baseline time point.

(B) MIT-T1, melodic intonation therapy (experimental group) after one month.

(C) ST-T0, speech therapy group (control group) on baseline time point.

(D) ST-T1, speech therapy (control group) after one month.

melodic input received, the more helpful it was to promote neural remodeling in a larger area of the brain. Extensive network expansion of FA and FN in the right hemisphere was observed in the MIT group (Figure 7), indicating that patients with better right brain integrity, even after left hemisphere damage, did better after receiving musical MIT therapy than those receiving language therapy alone. In the MIT group, there

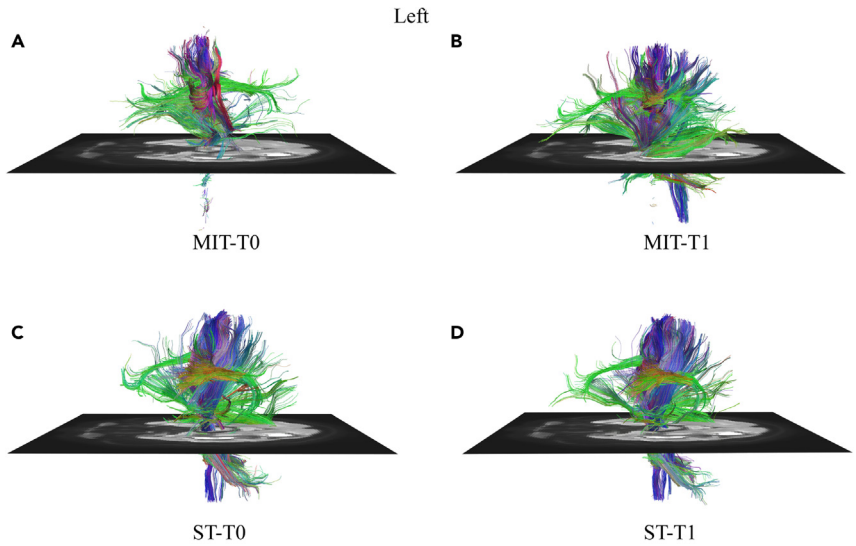


Figure 6. Comparison of neural plasticity of cerebral networks based on DTI 3D visible images in the left plane in patients with non-fluent aphasia after stroke in two groups; left, left plane

MIT, melodic intonation therapy group (experimental group); ST, speech therapy group (control group); T0, baseline time point, before intervention; T1, after one month of intervention.

(A) MIT-T0, melodic intonation therapy group (experimental group) at baseline time point.

(B) MIT-T1, melodic intonation therapy (experimental group) after one month.

(C) ST-T0, speech therapy group (control group) at baseline time point.

(D) ST-T1, speech therapy (control group) after one month.

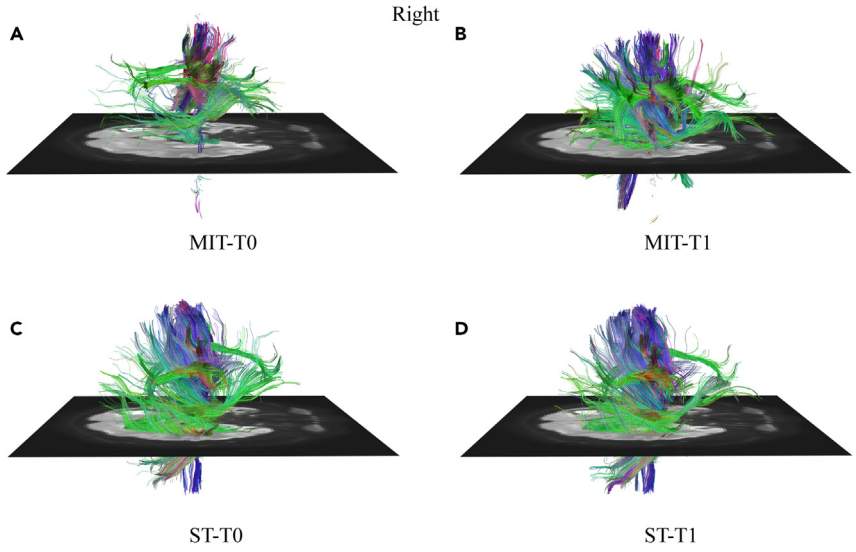


Figure 7. Comparison of neural plasticity of cerebral networks based on DTI 3D visible images in the right plane in patients with non-fluent aphasia after stroke in two groups; right, right plane

MIT, melodic intonation therapy group (experimental group); ST, speech therapy group (control group); T0, baseline time point, before intervention; T1, after one month of intervention.

(A) MIT-T0, melodic intonation therapy group (experimental group) at baseline time point.

(B) MIT-T1, melodic intonation therapy (experimental group) after one month.

(C) ST-T0, speech therapy group (control group) at baseline time point.

(D) ST-T1, speech therapy (control group) after one month.

was a global enhancement of networks in the right hemisphere, especially in the volume of white matter fiber tracts connecting the temporal and frontal language areas. After corresponding structural changes, patients in the MIT group showed higher scores of spontaneous speech expression and thematic dialogue. Regarding the intra-group effect, qualitative assessments of the MIT group after 22 MIT sessions were significantly better than those of the ST group, indicating that the melodic stimulation from music was more excitatory in the right inferior frontal gyrus and the bilateral temporal lobe network and more effectively improved language function.[34] Therefore, music, as the core therapeutic factor, dominated the rehabilitation of language function in MIT.

In addition, familiar music, especially old songs, was used during MIT, in addition to the use of formulated melodies. When the brain searches for and remembers words related to old song lyrics, it activates the right anterior cingulate cortex and the medial prefrontal cortex, which are important regions in the recall process. Listening to repetitive formulaic melodies coupled with the guidance of key phrases from old songs, this auditory–verbal interaction connection promoted the divergence enhancement of the language neural networks and improved language function in the MIT group.

Clinical practice guidance

In the process of music-based MIT for patients with non-fluent aphasia, the efficacy of language recovery is directly influenced by the number of musicalization factors. Specifically, the more severe the aphasia is, the longer MIT intervention time is needed, and the more musical elements are needed (such as melody, tonality, pitch, rhythm, timbre, harmony, vocal, and instruments). Patients with mild aphasia require fewer musical elements (such as tone + rhythm) and shorter sessions. The recommended dose is 30 min of daily training, with one month as the starting baseline. Therefore, in clinical practice, consultants should provide personalized treatment recommendations based on the severity of aphasia and the required amount of musical intervention (Figure 8).

Limitations of the study

As previously discussed, the study was limited in terms of sample size, with 22 participants prematurely withdrawing, which may have played a role in the variance in group assignments. This study only recruited 40 patients. The comparisons might have been more accurate if a blank was included in the control group to observe self-healing. Future studies may be able to observe therapeutic outcomes more accurately if they are conducted on a larger scale and include participants with each of the four types of non-fluent aphasia. There are different subtypes of non-fluent aphasia, although they belong to the same main category. In future studies, more samples should be included and different subtypes of aphasia should be classified and compared, which will make a comparison of effects clearer.

Musicalized MIT raises a number of questions that could be addressed in future studies, including the effects of music on bilateral hemispheric neuroplasticity and possible mirror neurons, the role of formulaic melody, the potential transfer effect of music and language, and the

Table 4. Region of interest (ROI) after MIT

		Area			Area			Area		
Lobe	Gyrus	Left	Right	FA	Left	Right	FN	Left	Right	Length
Frontal lobe	Superior frontal gyrus, SFG	1	2	medial area			dorsolateral area	1	2	medial area
		7	10	dorsolateral area	3		medial area	7		dorsolateral area
		9	12	medial area	9	10	medial area 10	11	12	medial area
			14					13	14	medial area
	Middle frontal gyrus, MFG		26	ventrolateral area	17		inferior frontal junction	15		dorsal area
					23		ventrolateral area			
	Inferior frontal gyrus, IFG							41	34	caudal area
	Orbital gyrus, OrG	41	42	medial area				43	42	medial area
								45	44	orbital area
								47		medial area
	Precentral gyrus, PrG	55		caudal dorsolateral area		54	head and face region	55	56	caudal dorsolateral area
			58	upper limb region		58	upper limb region			
		59	60	trunk region	59	60	trunk region			
Temporal lobe	Superior temporal gyrus, STG							69	70	medial area
	Middle temporal gyrus, MTG								84	rostral area
	Inferior temporal gyrus, ITG	95	96	medial lateral area						
		99	100	lateral area						
		101	102	ventral area						
	Parahippocampal, PhG		112	caudal area						
Parietal lobe	Inferior parietal lobule, IPL	125	126	rostral area				125		rostral area
			128	caudal area						
		131	132	postcentral gyrus				131		Postcentral gyrus
	Precuneus, Pcun				149	150	medial area	147		medial area7
			150	medial area		152	medial area			
		151	152	dorsomedial parieto-occipital sulcus				151		dorsamedial parieto-occipital sulcus
	Postcentral gyrus, PoG	161	160	trunk region		158	tongue and larynx region		162	trunk region
Insular lobe	Insular gyrus, INS		162						170	ventral dysgranular and granular insula
Limbic lobe	Cingulate gyrus, CG	181	182	ventral area				181		ventral area
									184	dorsolateral area
Occipital lobe	MedioVentral occipital	191	192	rostral cuneus gyrus				195	196	rostral lingual gyrus

(*Continued on next page*)

Table 4. *Continued*

		Area			Area			Area		
Lobe	Gyrus	Left	Right	FA	Left	Right	FN	Left	Right	Length
	MVOcO	193		caudal cuneus gyrus				197		ventromedial parieto-occipital sulcus
		197	198	ventromedial parieto-occipital sulcus						
	Lateral occipital cortex		208	medial superior occipital gyrus	199	200	middle occipital gyrus	207	208	medial superior occipital gyrus
	LOcC									
Subcortical nuclei	Hippocampus, Hipp		216	rostral hippocampus						
	Basal ganglia, BG							219	220	ventral caudate
		221	222	globus pallidus	227	228	dorsolateral caudate	221	222	globus pallidus
		225		ventromedial putamen				223	224	nucleus accumbens
								225	226	ventromedial putamen
								229	230	dorsolateral putamen

FA, FN, and length enhancement trends after music-based MIT intervention. The numbers in the table indicate the label number of brain regions.The numbers in the table indicate the number of brain regions, where odd numbers are left hemisphere regions, even numbers are left hemisphere regions, and the two are mirror correspondence.

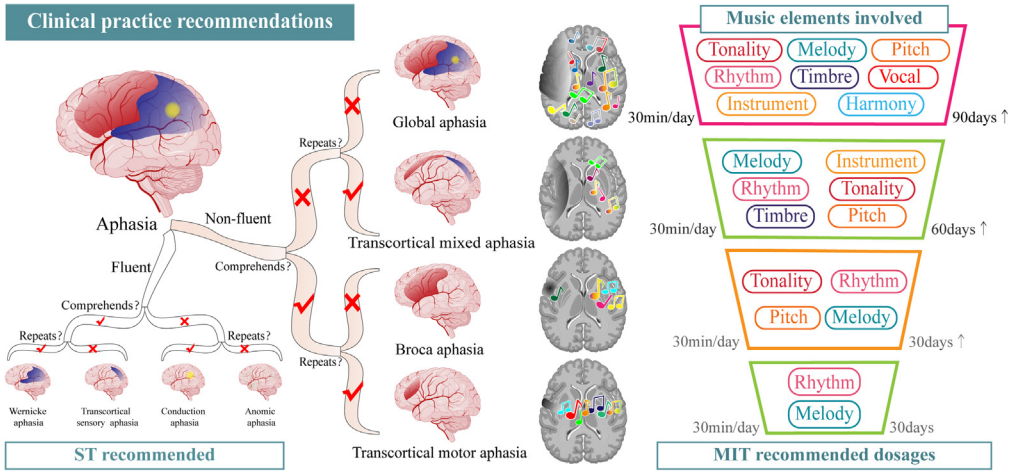


Figure 8. Clinical practice guidance in the process of music-based melodic intonation therapy (MIT) for patients with non-fluent aphasia

Different colors represent different musical elements. Global aphasia required the most musical elements, and the transcortical mixed aphasia, Broca's aphasia and transcortical motor aphasia use of musical elements decreased in turn. The MIT recommended dosage is 30min/day for 30 days to start line of the intervention. The lighter the color, the less the dose is. The darker the color, the higher is the dose.

relative role of music atmosphere and interpersonal. However, focusing on melody alone or language alone does not effectively reflect the multifaceted treatment approach of music therapy. Future research directions should not only focus on the cumulative effects of musicalized MIT but also observe the relationship between melody and phrase in the task state and focus on the heterogeneity of lesions. This will better distinguish between brain regions in response to music and functional processing and maximize the effects of music therapy.

Conclusions

Patients with non-fluent aphasia can benefit from MIT intervention through musical activities, especially in the early stages of the disease. Patients with severe aphasia are more likely to improve their language function if they receive an intervention including multiple music elements. The effects of clinical treatment can be enhanced through collaboration between clinicians and music therapists.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability
- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS
- METHOD DETAILS
  - Study design
  - Participants
  - Procedure
  - Interventions
  - Measurements
  - Statistical analysis
- QUANTIFICATION AND STATISTICAL ANALYSIS

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.107453.

ACKNOWLEDGMENTS

This research was supported by the China Rehabilitation Research Center (CRRC). We thank for Qingqing Feng and Ze Zhao who implemented the BDAE assessment and evaluation; Wenjia Teng, Mengyang Lu, Yinan Li, Linhan Yang, who supported music therapy – melodic

intonation therapy in the experimental group from the Music Therapy Center, CRRC. Thanks to all speech therapists in the Department of Speech Therapy; Department of Neurorehabilitation, CRRC; who provided technical support had greatly assisted the research. We would like to thank Yi Du, the Principal Investigator of the Chinese Academy of Sciences, for her guidance and support in 2020. We thank Charlesworth Author Services (https://www.cwauthors.com.cn/) for its linguistic assistance during the preparation of this manuscript. We thank BioRender.com for the support of the diagram drawing.

Funding: This research was supported by the National Natural Science Foundation of China Special research project "Music Intelligence Quantification and Brain Science Cognition Research" (No. T2341003). The Chinese Institute of Rehabilitation Sciences provided the start-up funding for this work through its Special Fund for Basic Scientific Research "Clinical and mechanism study of melodic intonation therapy for non-fluent aphasia after stroke" (grant number 2020CZ-10). There was no involvement by the funding sources in the conception and design of the study, the analysis and interpretation of the data, the writing of the paper, or the decision to submit the manuscript to a journal.

AUTHOR CONTRIBUTIONS

X.Z. was responsible for study design, patient allocation, protocol development, and main manuscript writing. Z.T. was responsible for data statistics, result description, and statistical chart drawing. J.L. is in charge of clinical guidance, X.L. is the chief director of NSFC project, and F.Y. is the general director of the NSFC project. All authors can directly access and verify the underlying data reported in the manuscript. The authors of this research articles are all from the academic team.

DECLARATION OF INTERESTS

This work does not contain any conflicts of interest; neither financial nor associative interest represents a conflict of interest.

INCLUSION AND DIVERSITY

We support inclusive, diverse, and equitable conduct of research.

Received: April 3, 2023
Revised: May 13, 2023
Accepted: July 19, 2023
Published: August 23, 2023

REFERENCES

1. Benjamin, E.J., Blaha, M.J., Chiuve, S.E., Cushman, M., Das, S.R., Deo, R., de Ferranti, S.D., Floyd, J., Fornage, M., Gillespie, C., et al. (2017). Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation *135*, e146–e603.
2. Bernhardt, J., Corbett, D., Dukelow, S., Savitz, S., Solomon, J.M., Stockley, R., Sunnerhagen, K.S., Verheyden, G., Walker, M., Murphy, M.A., et al. (2023). The International Stroke Recovery and Rehabilitation Alliance [J]. Lancet Neurol. *22*, 295–296.
3. Dickey, L., Kagan, A., Lindsay, M.P., Fang, J., Rowland, A., and Black, S. (2010). Incidence and profile of inpatient stroke-induced aphasia in Ontario, Canada. Arch. Phys. Med. Rehabil. *91*, 196–202.
4. World Stroke Organization. Learn about stroke. https://www.world-stroke.org/world-stroke-day-campaign/why-stroke-matters/learn-about-stroke.
5. Van Der Meulen, I., Van De Sandt-Koenderman, M.W.M.E., Heijenbrok, M.H., Visch-Brink, E., and Ribbers, G.M. (2016). Melodic Intonation Therapy in Chronic Aphasia: Evidence from a Pilot Randomized Controlled Trial. Front. Hum. Neurosci. *10*, 533. https://doi.org/10.3389/fnhum.2016.00533.
6. Fazio, P., Cantagallo, A., Craighero, L., D'Ausilio, A., Roy, A.C., Pozzo, T., Calzolari, F., Granieri, E., and Fadiga, L. (2009). Encoding of human action in Broca's area. Brain *132*, 1980–1988.
7. Mesulam, M.M., Coventry, C.A., Bigio, E.H., Sridhar, J., Gill, N., Fought, A.J., Zhang, H., Thompson, C.K., Geula, C., Gefen, T., et al. (2022). Neuropathological fingerprints of survival, atrophy and language in primary progressive aphasia. Brain *145*, 2133–2148.
8. Albert, M.L., Sparks, R.W., and Helm, N.A. (1973). Melodic intonation therapy for aphasia. Arch. Neurol. *29*, 130–131.
9. Zumbansen, A., Peretz, I., and Hébert, S. (2014). The Combination of Rhythm and Pitch Can Account for the Beneficial Effect of Melodic Intonation Therapy on Connected Speech Improvements in Broca's Aphasia. Front. Hum. Neurosci. *8*, 592.
10. Zhang, X., Li, J., and Du, Y. (2021). Melodic Intonation Therapy on Non-fluent Aphasia After Stroke: A Systematic Review and Analysis on Clinical Trials. Front. Neurosci. *15*, 753356.
11. Gentilucci, M., and Dalla Volta, R. (2008). Spoken language and arm gestures are controlled by the same motor control system. Q. J. Exp. Psychol. *61*, 944–957.
12. Norton, A., Zipse, L., Marchina, S., and Schlaug, G. (2009). Melodic intonation therapy: shared insights on how it is done and why it might help. Ann. N. Y. Acad. Sci. *1169*, 431–436.
13. Sparks, R., Helm, N., and Albert, M. (1974). Aphasia rehabilitation resulting from melodic intonation therapy. Cortex *10*, 303–316.
14. Ye, Q., Zhai, F., Chao, B., Cao, L., Xu, Y., Zhang, P., Han, H., Wang, L., Xu, B., Chen, W., et al. (2022). Rates of intravenous thrombolysis and endovascular therapy for acute ischaemic stroke in China between 2019 and 2020. The Lancet regional health. Western Pacific *21*, 100406.
15. Cortese, M.D., Riganello, F., Arcuri, F., Pignataro, L.M., and Buglione, I. (2015). Rehabilitation of aphasia: application of melodic-rhythmic therapy to Italian language. Front. Hum. Neurosci. *9*, 520.
16. Tabei, K.I., Satoh, M., Nakano, C., Ito, A., Shimoji, Y., Kida, H., Sakuma, H., and Tomimoto, H. (2016). Improved Neural Processing Efficiency in a Chronic Aphasia Patient Following Melodic Intonation Therapy: A Neuropsychological and Functional MRI Study. Front. Neurol. *7*, 148.
17. Popovici, M. (1995). Melodic intonation therapy in the verbal decoding of aphasics. Rom. J. Neurol. Psychiatr. *33*, 57–97.
18. Bonakdarpour, B., Hurley, R.S., Wang, A.R., Fereira, H.R., Basu, A., Chatrathi, A., Guillaume, K., Rogalski, E.J., and Mesulam, M.M. (2019). Perturbations of language network connectivity in primary progressive aphasia. Cortex *121*, 468–480.
19. Zumbansen, A., Peretz, I., and Hébert, S. (2014). Melodic intonation therapy: back to basics for future research. Front. Neurol. *5*, 7.
20. Breier, J.I., Randle, S., Maher, L.M., and Papanicolaou, A.C. (2010). Changes in maps of language activity activation following melodic intonation therapy using magnetoencephalography: two case studies. J. Clin. Exp. Neuropsychol. *32*, 309–314.
21. Van der Meulen, I., van de Sandt-Koenderman, M.E., and Ribbers, G.M. (2012). Melodic Intonation Therapy: present

controversies and future opportunities. Arch. Phys. Med. Rehabil. *93*, S46–S52.

22. Wan, C.Y., Zheng, X., Marchina, S., Norton, A., and Schlaug, G. (2014). Intensive therapy induces contralateral white matter changes in chronic stroke patients with Broca's aphasia. Brain Lang. *136*, 1–7.
23. Behaghel, E., and Zumbansen, A. (2022). Singing for the Rehabilitation of Acquired Neurogenic Communication Disorders: Continuing the Evidence Dialogue with a Survey of Current Practices in Speech-Language Pathology. Health Care *10*, 1010.
24. GBD 2019 Stroke Collaborators (2021). Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. *20*, 795–820.
25. Chow, I., and Brown, S. (2018). A Musical Approach to Speech Melody. Front. Psychol. *9*, 247.
26. Zhang, X.Y., Yu, W.Y., Teng, W.J., Lu, M.Y., Wu, X.L., Yang, Y.Q., Chen, C., Liu, L.X., Liu, S.H., and Li, J.J. (2021). Effectiveness of Melodic Intonation Therapy in Chinese Mandarin on Non-fluent Aphasia in Patients After Stroke: A Randomized Control Trial. Front. Neurosci. *15*, 648724.
27. Seligowski, A.V., Misganaw, B., Duffy, L.A., Ressler, K.J., and Guffanti, G. (2022). Leveraging Large-Scale Genetics of PTSD and Cardiovascular Disease to Demonstrate Robust Shared Risk and Improve Risk Prediction Accuracy. Am. J. Psychiatr. *179*, 814–823.
28. Fong, M.W.M., Van Patten, R., and Fucetola, R.P. (2019). The Factor Structure of the Boston Diagnostic Aphasia Examination, Third Edition. J. Int. Neuropsychol. Soc. *25*, 772–776.
29. Sparks, H. (2008). Melodic intonation therapy. In Language Intervention Strategies in Aphasia and Related Neurogenic Communication Disorders, R. Chapey, ed. (LippincottWilliams &Wilkins), pp. 837–851.
30. Sihvonen, A.J., Särkämö, T., Leo, V., Tervaniemi, M., Altenmüller, E., and Soinila, S. (2017). Music-based interventions in neurological rehabilitation. Lancet Neurol.. S1474442217301680.
31. Sihvonen, A.J., Ripollés, P., Leo, V., Saunavaara, J., Parkkola, R., Rodríguez-Fornells, A., Soinila, S., and Särkämö, T. (2021). Vocal music listening enhances post-stroke language network reorganization. eNeuro *8*. ENEURO.0158-21.2021.
32. Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A.R., et al. (2016). The Human Brainnetome Atlas: A New Brain Atlas Based on Connectional Architecture. Cerebr. Cortex *26*, 3508–3526.
33. Zatorre, R.J., and Gandour, J.T. (2008). Neural specializations for speech and pitch: moving beyond the dichotomies. Philos. Trans. R. Soc. Lond. B Biol. Sci. *363*, 1087–1104.
34. Vines, B.W., Norton, A.C., and Schlaug, G. (2011). Non-invasive brain stimulation enhances the effects of melodic intonation therapy. Front. Psychol. *2*, 230.
35. Belin, P., Van E, P., Zilbovicius, M., Remy, P., FranFois, C., Guillaume, S., and Samson, Y. (1991). Recovery from nonfluent aphasia after melodic intonation therapy. Hum. Mov. Sci. *10*, 315–334.
36. Akanuma, K., Meguro, K., Satoh, M., Tashiro, M., and Itoh, M. (2016). Singing can improve speech function in aphasics associated with intact right basal ganglia and preserve right temporal glucose metabolism: Implications for singing therapy indication. Int. J. Neurosci. *126*, 39–45.
37. Martzoukou, M., Nousia, A., Nasios, G., and Tsiouris, S. (2021). Adaptation of Melodic Intonation Therapy to Greek: A Clinical Study in Broca's Aphasia With Brain Perfusion SPECT Validation. Front. Aging Neurosci. *13*, 664581.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
NIH stroke scale, NIHSS	Seligowski et al.[27]	https://www.ninds.nih.gov/
BDAE	Fong et al.[28]	https://strokengine.ca/en/assessments/
PHILLPS Ingenia 3.0T fMRI	Zhang et al.[26]	http://www.philips.com.tw/healthcare/product/HC889226
SPSS 23.0	Behaghel et al.[23]	https://ibm-spss-statistics.software.informer.com/23.0/
MATLAB PANDA	Zhang et al.[26]	http://www.nitrc.org/projects/panda
DTI	Vines et al.[34]	https://www.trackvis.org/
Brainnetome Atlas	Fan et al.[32]	http://atlas.brainnetome.org/

RESOURCE AVAILABILITY

Lead contact

Jianjun Li crrclijj@163.com is responsible for communication with the journal before and after publication and is the arbiter of disputes, including concerns related to reagents or resource sharing. All the authors are willing to distribute all materials, datasets, and protocols used in the manuscript. Jianjun Li holds responsibility for responding to requests and providing information regarding reagents and resource sharing.

Materials availability

This study did not generate new unique reagents.

Data and code availability

- The data generated and/or analyzed during the current study can be accessed from the lead contact corresponding author upon reasonable request. The registered clinical trial number is ChiCTR2000037871.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request a bullet point for Data/Code, one for all other items.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

This pilot clinical trial used a before-and-after test design including two groups—an experimental group (n = 20) and a control group (n = 20). The study was an open-label pilot study; participants knew they were engaging in a clinical trial and the grouping. All individuals were Asian and native speakers of Chinese. The demographic characteristics of the participants, including gender, age, time of injury, and type of aphasia are described in Table 1. This study was in compliance with the national legislation and it was performed according to the ethical guidelines of the Declaration of Helsinki. The research protocol was approved by the Ethics Committee of the CRRC (Approval number: 2020-013-1; April 1, 2020; Document S1), and participants or their families provided written informed consent (Document S2) before commencing the study. The trial was registered with the Clinical Trial Registry (Registration No. ChiCTR2000037871) on September 3rd, 2020.

METHOD DETAILS

Study design

The study was an open-label pilot clinical study; participants knew they were engaging in a clinical trial and the grouping. The formula n = $Z2 \cdot \sigma 2/d2$ is calculated according to the sample size. Z is the confidence interval, taking the value of 90%. Σ is the standard error; D is the error range (0.15), and the minimum sample size n=31 is obtained. Therefore, this pilot study meets the requirement of minimum sample size. All individuals were divided into two groups - an experimental group and a control group. Computer-generated sequences were used (Excel 2013, US, Washington, Seattle, Microsoft Office) to divide into two groups. An anonymous data analyst did not know which data set was being tested and analyzed. Speech therapy was given to the control group while MIT was given to the experimental group. From April 2020 to November 2022, the study was conducted at the China Rehabilitation Research Center (CRRC) China.

Participants

Sixty-two patients with stroke hospitalized in Beijing Bo'ai Hospital, China Rehabilitation Research Center, were selected. 40 participants completed the trial. Twenty-two participants withdrew from the trial; 13 withdrew because of the COVID-19 pandemic, 6 because of

intermediate referrals, and 3 because of personal reasons. Patient recruitment was conducted from January 2020 to December 2022. Participants in the experimental (MIT) group were, on average, 50.15 years old (SD 15.44), and control group participants (ST) were, on average, 51.6 years (SD 14.27). Eleven participants (55%) in the experimental group had a diagnosis of ischemic stroke and 9 (45%) were diagnosed with hemorrhagic stroke; the mean time since injury was 2.3 months (SD 1.29); eight control participants (40%) were diagnosed with ischemic stroke and 12 (60%) with hemorrhagic stroke, and the mean time since injury was 1.8 months (SD 1.39). Nine (45%) participants in the MIT group were diagnosed with complete aphasia, four (20%) with Broca's aphasia, three (15%) with transcortical mixed aphasia, and four (20%) with transcortical motor aphasia. Seven control participants (35%) were diagnosed with global aphasia, three (15%) with Broca's aphasia, two (10%) with transcortical mixed aphasia, and eight (40%) with transcortical motor aphasia.

Procedure

Participants were first screened by neurorehabilitation physicians. Patients diagnosed with mild-to-moderate aphasia and severe aphasia on the 9th language score of the NIHSS were referred to the departments of speech and of music therapy. Once the participant and their family members provided written informed consent, participants were evaluated by a professional evaluator for BDAE to determine the score of non-fluent aphasia. The participants was then scheduled for pre-intervention fMRI-DTI examination. The researchers began assigning patients, using a computer-generated sequence (Excel 2013, Microsoft Office, Seattle, Washington, USA) to randomly assign patients to two groups. The experimental group received MIT from a registered music therapist for 4 weeks, while the control group received ST from a speech therapist for 4 weeks.

Interventions

For both MIT and ST, each patient trained for 30 minutes at a session, five sessions per week, 4weeks. To ensure the quality of the training process, MIT therapists were trained in Neurological Music Therapy (NMT) and licensed as registered music therapists. ST professionals who were licensed as rehabilitation therapists conducted the ST training process.

Measurements

Prior to the initiation of treatment, participants were assessed at baseline by a professional evaluator using the BDAE and fMRI- DTI. A second BDAE and DTI test were performed after 4 weeks of therapy to observe behavioral and imaging changes.

Statistical analysis

The data were analyzed using SPSS 23.0 for comparisons between pre- and post-treatment. A paired t-test was used if data were normally distributed and the variance was homogenous; p-value correction was used if data were normally distributed and the variance was not homogenous; and Wilcoxon signed-rank test was used if data were not normally distributed. For comparisons between the two groups, independent-samples t-tests were performed if the data were normally distributed and the variance was homogenous; for normally distributed data with nonhomoegenous variance, p-value-correction was used; if the data were not normally distributed, the U test was used to calculate the statistical value. P-values < 0.05 were considered statistically significant.

QUANTIFICATION AND STATISTICAL ANALYSIS

Statistical analyses were performed on each of the STAR Methods sections.