Right C7 neurotomy at the intervertebral foramen plus intensive speech and language therapy versus intensive speech and language therapy alone for chronic post-stroke aphasia: multicentre, randomised controlled trial

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ABSTRACT

OBJECTIVE

To evaluate whether right neurotomy of the seventh cervical nerve (C7) at the intervertebral foramen plus intensive speech and language therapy (SLT) improves language function compared intensive SLT alone in patients with chronic aphasia after stroke.

DESIGN

Multicentre, assessor blinded, randomised controlled trial.

SETTING

Four centres in mainland China.

PARTICIPANTS

50 adults aged 40-65 years with aphasia for more than one year after a single left hemispheric stroke.

INTERVENTIONS

Participants were randomised 1:1 to receive either C7 neurotomy plus three weeks of intensive SLT or three weeks of intensive SLT only, stratified by treatment centre.

MAIN OUTCOME MEASURES

The primary outcome was change in score on the 60 item Boston naming test (BNT, scores 0-60, with higher scores indicating better naming function) from baseline to one week after C7 neurotomy plus intensive SLT for three weeks or intensive SLT for three weeks after deferral for one week (control group). Secondary outcomes included change in severity of aphasia using the aphasia quotient, calculated using the western aphasia battery, and patient reported outcomes on quality of life and depression after stroke.

RESULTS

From 25 July 2022 to 31 July 2023, 322 out of 1086 patients received a diagnosis of post-stroke aphasia and were screened for eligibility. 50 eligible participants were randomly assigned to treatment groups (25 in each). Mean increase in BNT score was 11.16 points in the neurotomy plus SLT group and 2.72 points in the control group at one month (difference 8.51 points, 95% confidence interval (CI) 5.31 to 11.71, P<0.001). The between group difference in BNT score remained stable at six months (difference 8.26 points, 4.16 to 12.35, P<0.001). In addition, the aphasia quotient improved significantly in the neurotomy plus SLT group versus control group (difference at one month 7.06 points, 4.41 to 9.72, P<0.001), as did patient reported activities of daily living and post-stroke depression. No treatment related severe adverse events were reported.

CONCLUSIONS

C7 neurotomy plus three weeks of intensive SLT was associated with a greater improvement in language function compared with three weeks of intensive SLT alone over a period of six months. No severe adverse events or long term troublesome symptoms or functional loss were reported.

TRIAL REGISTRATION

Chinese Clinical Trial Register ChiCTR2200057180.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Chronic aphasia after stroke is challenging to treat

Intensive speech and language therapy (SLT) has been a main treatment for patients with chronic aphasia, but improvements in efficacy are needed

No technology has shown an add-on and sustained effect based on intensive SLT in improving language function of patients with chronic aphasia

WHAT THIS STUDY ADDS

This study proposed a new treatment, right neurotomy of the seventh cervical nerve (C7) at the intervertebral foramen, for patients with chronic aphasia after left hemispheric stroke

C7 neurotomy plus three weeks of intensive SLT significantly improved language function compared with intensive SLT alone in patients with aphasia after left hemispheric stroke for more than one year

No surgery related additional severe adverse events or long term troublesome symptoms were reported

Introduction

Cerebrovascular events are not only life threatening but also result in chronic sequelae, with aphasia being one of the most common conditions.[1 2] More than one third of people are estimated to experience aphasia during the initial acute stage of hemispheric stroke, and more than 60% continue to be affected for more than a year, referred to as chronic post-stroke aphasia.[3 4] Chronic aphasia represents disability in several aspects of language, severely affecting communication, self-care,

and return to usual life or work and resulting in a heavy economic burden.[5] An estimated 8-9% of stroke related healthcare costs during the first year after stroke are due to aphasia.[6] How to improve the language function in these patients remains a huge challenge.

Since the left hemisphere is the dominant region for language processing, around 80% of patients with aphasia due to left hemispheric stroke also experience right spastic arm paralysis, whereas the other 20% experience aphasia only.[7 8] Recently, the use of contralateral C7 nerve transfer surgery to treat spastic arm paralysis due to chronic cerebral neurological injury has become popular worldwide.[9] Patients with left sided stroke and spastic arm paralysis combined with aphasia often report improved language function after C7 nerve transfer surgery, especially in naming objects.[10] As deficit in naming ability is a common symptom in people with aphasia, this phenomenon possesses important clinical clues. Therefore, after step-by-step research, we designed right sided C7 neurotomy at the intervertebral foramen as a potential treatment for post-stroke aphasia (see video 1 showing procedure).[11 12] As intensive speech and language therapy (SLT) is a standard treatment for chronic post-stroke aphasia,[13] we hypothesised that a combination of C7 neurotomy plus intensive SLT might have a cumulative effect on improving language function. We therefore performed a multicentre randomised controlled trial to assess the effectiveness and safety of C7 neurotomy plus three weeks of intensive SLT compared with three weeks of intensive SLT only for improving naming ability in patients with chronic aphasia after a left hemispheric stroke, and to assess neuroplasticity in the brain.

Methods

Study design

This was a multicentre, assessor blinded, randomised controlled trial in four centres in Shanghai, China. The study protocol is published elsewhere.[14]

Participants

We recruited patients aged 40-65 years who spoke fluent Chinese before stroke. Patients were eligible for inclusion if they had aphasia for more than 12 months after a single onset of infarction or haemorrhage of the left hemisphere confirmed by magnetic resonance imaging (MRI), manifesting as an inability to express themselves or difficulties with verbal communications for more than one year. Aphasia required diagnosis by two doctors and a score of <93.8 on the aphasia quotient calculated by the Chinese version of the western aphasia battery and classified as level ≥1 in the Boston diagnostic aphasia examination. Participants were required to have basic comprehension and to fully understand the study design and cooperate with the treatment plan. Patients were excluded if they had neurodegenerative disease, traumatic brain injury, a history of aphasia before the last onset of stroke, severe motor speech disorder, hearing impairment, or received intensive post-stroke rehabilitation therapy within four weeks before recruitment (see supplementary appendix for inclusion and exclusion criteria).

Randomisation and masking

After screening, eligible patients were randomly assigned in a 1:1 ratio to C7 neurotomy plus intensive SLT or to intensive SLT only. Randomisation was stratified according to trial centre without using blocks.[14] The statistician responsible for generating the randomisation sequence was not involved in patient enrolment. An independent third party (Trial Data Pharmaceutical Technology, Shanghai, China) carried out randomisation through a centralised interactive web based randomisation system. Investigators randomly assigned patients through the online system and disclosed allocation to the patients.

Neither the patients nor clinical investigators providing the interventions were masked to group allocation. However, the outcome assessors were blinded. Patients undergoing language and vocal evaluations at each follow-up were videotaped. A third party team composed of two independent evaluators and one monitor then centrally evaluated the recordings. The evaluators and monitor were unaware of patients' identities, treatment assignments, time points, or location of clinical sites. Patients wore a cervical collar during evaluations to conceal any surgical scars.

Interventions

The C7 neurotomy procedure is described in the published protocol and shown schematically in supplementary figure S1 and the embedded video (also in supplementary file as video S1). Briefly, an incision was made at the medial side of the sternocleidomastoid muscle on the right side and the C7 nerve root exposed as proximally as possible and then sectioned at the intervertebral foramen. The distal cut end of the C7 nerve was close to the sternocleidomastoid muscle for use as nerve end recipient if patients had verbally expressed a willingness to undergo nerve transfer.[9 15] Surgeons experienced in brachial plexus surgery and trained in Huashan Hospital's standard surgical protocols performed the C7 neurotomies.

In the neurotomy plus intensive SLT group, three weeks of intensive SLT was initiated one week after surgery. In the SLT only group, three weeks of intensive SLT was initiated after one week's deferral (see supplementary appendix figure S2 for trial design). Trained therapists provided both groups with the same intensive SLT for at least 45 minutes twice daily for five days a week.[13 16] The SLT also included additional self-administrated language specific training for one hour daily. Patients at all the study centres received intensive SLT from qualified rehabilitation therapists trained in Huashan Hospital's standard protocol.

Outcomes

The primary outcome was change in total score on the 60 item Boston naming test (BNT) of a validated

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Chinese version from baseline to one week after C7 neurotomy plus three weeks of intensive SLT in the intervention group or from three weeks of intensive SLT after deferral for one week in the control group.[17 18] BNT included 60 monochrome pictures showing objects used in daily life. Participants scored 1 point if they spontaneously recognised and correctly pronounced the object, otherwise they scored 0 (scores 0-60, with higher scores indicating better function).

Secondary outcomes included change in BNT score from baseline to three days after neurotomy in the intervention group or three days from start of deferral of intensive SLT in the control group and change from baseline to 24 weeks after initiation of intensive SLT in both groups (see supplementary figure S2). The other secondary outcomes included changes in the aphasia quotient as evaluated by a Chinese version of the western aphasia battery, which weighted the average of the first four subtest scores (scores 0-100, with higher scores indicating better function). We also assessed patient reported outcomes to evaluate changes in activities of daily living measured using the Barthel index and depression after stroke measured using the stroke aphasic depression questionnaire-hospital version. The Barthel index contains 10 questions and measures the ability to perform common activities of daily living (score 0-100, with higher scores indicating better quality of life).[19] The stroke aphasic depression questionnaire scale evaluated post-stroke depression using 10 questions (each question comprises four options scoring from 0 to 3, with a total score of 30, larger scores indicating a larger tendency for depression) answered by the patient's next of kin or care giver.[20] Total scores derived from patient reported outcomes were treated as continuous variables. We also used the aphasia adapted speech language function assessment using the international classification of functioning, disability, and health to detect any physiological or structural changes relating to voice function.[21] Secondary outcomes were evaluated at baseline, three days, one month, and six months.

The overt picture naming task was used during functional MRI to assess the mechanism for central plasticity accompanying functional recovery.[22] Patients were asked to vocally name the monochrome objects in each picture presented on a screen during scanning. The supplementary appendix describes the design and analysis protocol.

Safety outcomes included adverse events, changes in motor function, spasticity of the right elbow, wrist, and fingers, and changes in sensory functions assessed by tactile sensory threshold and two point discrimination of the right thumb, index fingers, and middle fingers over a period of six months. Motor function included muscle power measured using the Medical Research Council's scale (grades 0-5, with higher grades indicating better muscle power) and range of motion of the elbow, wrist, and fingers. Spasticity was measured with the modified Ashworth scale at the elbow, wrist, and fingers (scores 0-4, with higher scores indicating more spasticity).[23]

Statistical analysis

Based on our pilot study[12] and a systematic review on intensive SLT,[24] we assumed a mean difference of 5.5 points in change of BNT score between the neurotomy and intensive SLT group and control group. Therefore, we estimated that a sample size of 50 participants (25 in each group), under the assumption of a 20% dropout rate, would provide 80% power to detect a mean difference of 5.5 (standard deviation 6.2) points between groups on the BNT score with a two sided α level of 0.05. We considered a between group difference in functional improvement of 5.5 points to be of clinical importance, although 5.5 points did not represent the threshold for minimal clinically important difference. This sample size is of good credibility, would allow conclusions to be drawn at minimal risk to patients, and is in accordance with other randomised controlled trials on surgical treatments.[25 26]

We performed efficacy analyses for primary and secondary outcomes in the intention-to-treat population, comprising all randomised participants who received any treatment and had at least one complete BNT score at follow-up. Primary outcome data were complete, with no imputation required. Descriptive statistics were used to report the characteristics of the participants at baseline. Analysis of covariance was used to compare changes in continuous outcomes between the two groups from baseline to one month, adjusting for baseline measures and study centres as covariates. For categorical variables, we used Cochran-Mantel-Haenszel χ^2 or Fisher's exact tests for between group comparisons. Prespecified subgroup analyses included study centre, type of stroke, type of aphasia, and severity of aphasia, and post hoc subgroup analyses of age, sex, and duration of aphasia.

For sensitivity analysis, we assessed the longitudinal BNT and western aphasia battery score using a mixed model. Fixed factors were treatment group, treatment group and time interaction, clinical centre, and score at baseline. To account for dependent variables in the repeated measures, we included a patient specific random intercept. Using this model, we estimated marginal means for each time point and treatment group. Additional sensitivity analyses for the primary outcome were carried out in a per protocol dataset. This dataset included all participants who completed the study treatment without major protocol deviations. The statistical analysis plan provides detailed information on the analyses. All hypothesis tests were two sided, and statistical significance was set at $P<0.05$. All statistical analyses were performed using R software (version 4.3.2).

For assessment of functional MRI data, images of each patient were analysed using FMRIB Software Library (version 6.00) FEAT (FMRI Expert Analysis Tool) first level analysis.[27] After following standard preprocessing procedures (eg, high pass filtering,

motion correction, see supplementary file), we performed a univariate general linear model analysis for each patient and calculated the contrast between overt picture naming and rest interval until the next task. A whole brain correlation analysis was performed between β estimate (of overt picture naming greater than rest) and BNT score for each group at each time point (baseline and one month and six months after surgery). The threshold for the resulting correlation maps was P<0.005 and cluster corrected at P<0.05. The final results include clusters at the whole brain level containing more than 150 contiguous voxels and remaining after cluster correction.

Patient and public involvement

No patients or members of the public were involved in the design, conduct, reporting, or dissemination of this research. Available funding was specifically designated for clinical implementation and data acquisition, with no dedicated resources allocated for patient and public involvement.

Results

Characteristics of participants

Between 25 July 2022 and 31 July 2023, a total of 322 of 1086 patients received a diagnosis of post-stroke aphasia and were screened for eligibility. Overall, 251

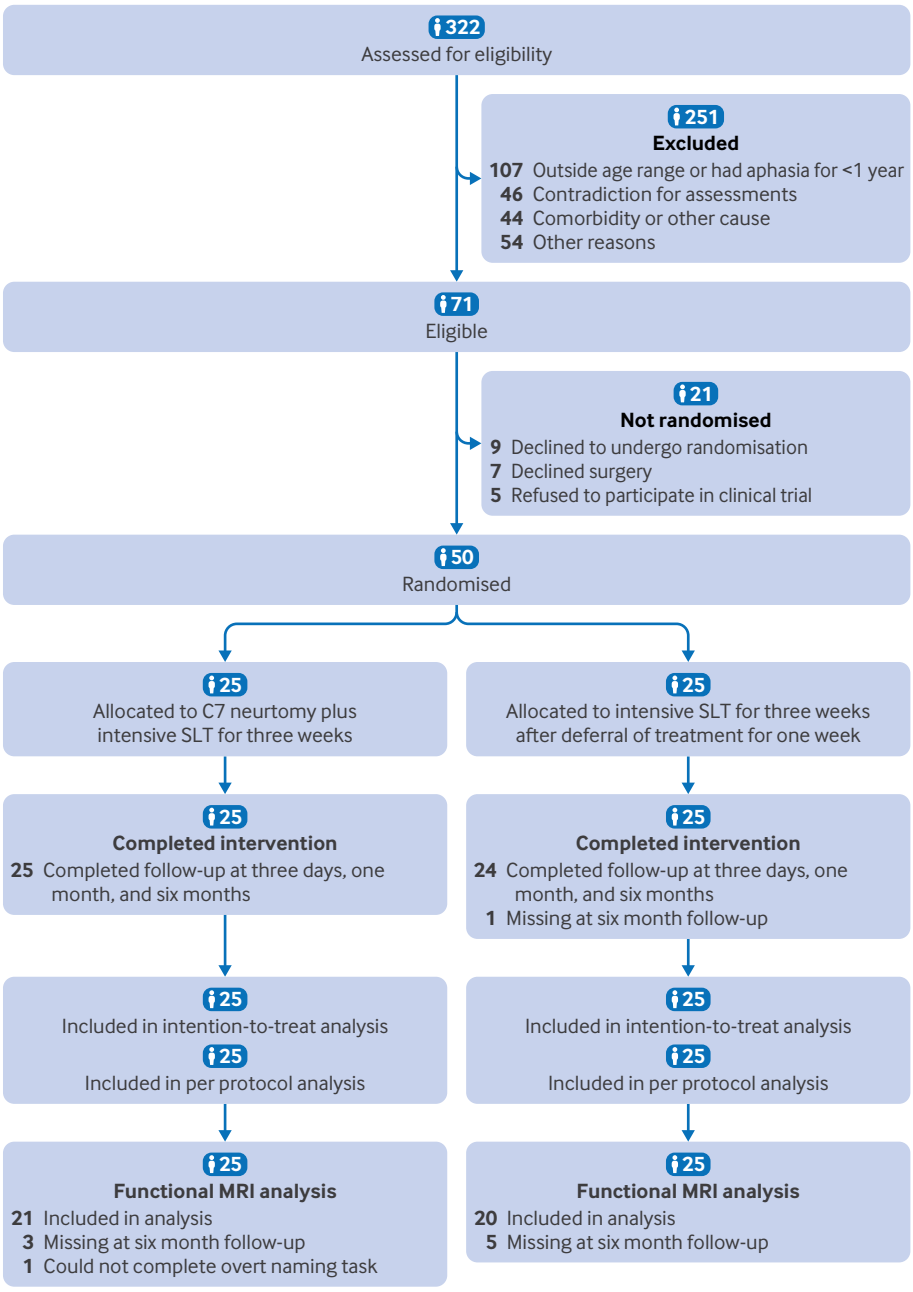

Fig 1 | Flow chart of participants through study. C7 neurotomy=right neurotomy of the seventh cervical nerve at the intervertebral foramen; MRI=magnetic resonance imaging; SLT=speech and language therapy

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Table 1 | Baseline characteristics of participants with chronic aphasia after stroke assigned to receive right C7 neurotomy plus intensive SLT or intensive SLT alone. Values are number (percentage) unless stated otherwise

Characteristics	C7 neurotomy+intensive SLT (n=25)	Intensive SLT (n=25)
Age at consent (years):		
Mean (SD)	53.0 (6.3)	52.1 (7.5)
Median (IQR)	52.7 (47.8-58.1)	51.8 (46.0-57.8)
Time from neurological injury to trial entry (months):		
Mean (SD)	39.7 (28.2)	36.2 (33.9)
Median (IQR)	28.8 (21.2-45.0)	25.3 (17.7-37.6)
Sex:		
Men	20 (80.0)	19 (76.0)
Women	5 (20.0)	6 (24.0)
Type of stroke:		
Haemorrhagic	13 (52.0)	12 (48.0)
Ischaemic	12 (48.0)	13 (52.0)
Type of aphasia:		
Non-fluent	23 (92.0)	22 (88.0)
Fluent	2 (8.0)	3 (12.0)
BDAE score*:		
1	18 (72.0)	19 (76.0)
≥2	7 (28.0)	6 (24.0)
Spastic arm paralysis:		
Yes	21 (84.0)	21 (84.0)
No	4 (16.0)	4 (16.0)
BNT score†:		
Mean (SD)	21.20 (12.52)	22.16 (12.77)
Median (IQR)	19.00 (12.00-27.00)	22.00 (13.00-30.00)
WAB-AQ score‡:		
Mean (SD)	48.38 (15.49)	49.77 (13.92)
Median (IQR)	49.50 (38.90-55.50)	49.10 (45.50-57.00)
Barthel index§:		
Mean (SD)	83.80 (12.27)	84.80 (16.10)
Median (IQR)	85.00 (75.00-95.00)	90.00 (75.00-100.00)
SADQ-H10 score¶:		
Mean (SD)	4.28 (2.51)	4.36 (2.74)
Median (IQR)	4.00 (3.00-6.00)	4.00 (3.00-6.00)

Percentages may not total 100 owing to rounding.
BDAE=Boston diagnostic aphasia examination; BNT=Boston naming test; C7 neurotomy=right neurotomy of the seventh cervical nerve at the intervertebral foramen; IQR=interquartile range; SADQ-H10=stroke aphasic depression questionnaire hospital version; SLT=speech and language therapy; WAB-AQ=western aphasia battery-aphasia quotient.
*Used to diagnose aphasia and related disorders, with five grades in total.
†Measures language impairment (scores 0-60, with higher scores indicating better function).
‡Measures language ability (scores 0-100, with higher scores indicating better function). Score is weighted average of all subtest scores relating to spoken language.
§Measures degree of assistance an individual requires on 10 mobility and self-care activities of daily living items (scores 0-100, with higher scores indicating better functional independence).
¶Measures depression after stroke, with numerical values assigned to observer selections (range 0-3, with higher scores indicating more post-stroke depression symptoms).

patients were excluded for being outside the age range for participation in the study or having aphasia for less than one year (n=107), having contradictions for assessments (n=46), having comorbidities or aphasia due to other causes (n=44), and other reasons (n=54). Among 71 eligible patients, 50 were enrolled and randomly allocated to undergo C7 neurotomy plus three weeks of intensive SLT (n=25) or intensive SLT for three weeks after deferral for one week (n=25). Twenty one patients were not enrolled: nine declined to undergo randomisation, seven declined surgery, and five did not want to participate in a clinical trial. Figure 1 shows the flow chart of participants through the study.

Table 1 shows the personal characteristics of the participants at baseline. The median interval from neurological injury to entry into the trial was 28.8 months (interquartile range (IQR) 21.2-45.0 months) in the neurotomy plus intensive SLT group and 25.3 (17.7-37.6) months in the control group. Based on classification criteria of the Chinese version of the western aphasia battery, 45 patients had non-fluent aphasia (including 37 with Broca's aphasia) and five had fluent aphasia. Among all the 50 patients, 42 had spastic arm paralysis with an average spasticity of around 1 degree (mild spastic), similar to the population in our previous published studies.[9 10]

Primary outcome

Mean change in BNT score from baseline to one month was 11.16 (SD 7.10) points in the neurotomy plus intensive SLT group versus 2.72 (3.40) points in the control group, with a significantly greater improvement in the neurotomy plus intensive SLT group (group difference 8.51, 95% confidence interval (CI) 5.31 to 11.71, P<0.001) (table 2, fig 2, fig 3, and supplementary

Table 2 | Changes in primary and secondary outcomes from baseline in participants with chronic aphasia after stroke assigned to receive C7 neurotomy plus intensive SLT or intensive SLT alone. Values are mean (standard deviation) unless stated otherwise

Outcomes	C7 neurotomy+intensive SLT (n=25)	Intensive SLT (n=25)	Mean difference* (95% CI)	P value
Primary outcome				
Change in BNT score at one month	11.16 (7.10)	2.72 (3.40)	8.51 (5.31 to 11.71)	<0.001
Secondary outcomes				
Change in BNT score at three days	5.28 (3.45)	0.20 (2.02)	5.08 (3.44 to 6.71)	<0.001
Change in BNT score at six months	10.24 (8.75)	2.08 (3.99)	8.26 (4.16 to 12.35)	<0.001
Change in WAB-AQ score at three days:				
Total aphasia quotient	6.88 (3.09)	0.97 (3.39)	5.82 (4.00 to 7.64)	<0.001
Spontaneous speech	1.44 (1.16)	−0.04 (0.54)	1.41 (0.90 to 1.92)	<0.001
Comprehension	0.41 (0.66)	−0.05 (0.57)	0.44 (0.10 to 0.78)	0.01
Repetition	0.68 (0.68)	0.33 (0.89)	0.39 (−0.05 to 0.83)	0.08
Naming	0.91 (0.64)	0.24 (0.80)	0.66 (0.25 to 1.08)	0.002
Change in WAB-AQ score at one month:				
Total aphasia quotient	11.14 (5.44)	3.97 (3.69)	7.06 (4.41 to 9.72)	<0.001
Spontaneous speech	2.16 (1.49)	0.20 (0.76)	1.90 (1.21 to 2.59)	<0.001
Comprehension	0.67 (0.70)	0.27 (0.55)	0.38 (0.03 to 0.72)	0.03
Repetition	1.35 (0.82)	0.97 (0.80)	0.44 (0.04 to 0.84)	0.03
Naming	1.39 (0.95)	0.54 (0.84)	0.84 (0.33 to 1.36)	0.002
Change in WAB-AQ score at six months:				
Total aphasia quotient	9.14 (5.07)	3.15 (4.61)	6.05 (3.12 to 8.97)	<0.001
Spontaneous speech	2.08 (1.35)	0.13 (0.97)	1.96 (1.24 to 2.68)	<0.001
Comprehension	0.70 (0.77)	0.03 (0.69)	0.65 (0.24 to 1.07)	0.003
Repetition	0.87 (0.91)	0.79 (1.24)	0.15 (−0.48 to 0.78)	0.63
Naming	0.92 (0.82)	0.62 (0.89)	0.30 (−0.19 to 0.80)	0.23
Change in Barthel index:				
Three days	−1.60 (5.15)	−0.40 (4.31)	−1.28 (−3.95 to 1.39)	0.34
One month	3.00 (6.92)	−1.20 (7.26)	4.12 (0.23 to 8.00)	0.04
Six months†	5.00 (7.07)	0.87 (7.64)	3.93 (0.38 to 7.49)	0.03
Change in SADH-Q10 score:				
Three days	0.32 (1.46)	−0.24 (1.81)	0.55 (−0.37 to 1.46)	0.24
One month	−0.72 (2.21)	−0.16 (2.21)	−0.60 (−1.66 to 0.47)	0.27
Six months	−1.64 (1.52)	−0.43 (1.65)	−1.28 (−2.01 to −0.54)	0.001

ANCOVA=analysis of covariance; BNT=Boston naming test; CI=confidence interval; C7 neurotomy=right neurotomy of the seventh cervical nerve at the intervertebral foramen; SADQ-H10=stroke aphasic depression questionnaire hospital version; SLT=speech and language therapy; WAB-AQ=western aphasia battery-aphasia quotient.
Three days is from surgery in the C7 neurotomy plus intensive SLT group and three days from start of deferral of intensive SLT in the control group. One month is from surgery or from start of deferral of intensive SLT. Six months is from initiation of intensive SLT.
Total scores are 20 points for spontaneous speech and 10 points each for comprehension, repetition; and naming.
*Adjusted mean changes from baseline to three days, one month, and six months based on ANCOVA, with the model adjusted for baseline values and study centre as covariates. The confidence intervals and P value for secondary outcomes have not been adjusted for multiplicity.
†Owing to heteroscedasticity of residuals, a weighted least squares adjusted ANCOVA model was used to estimate the mean group difference and P value.

videos 2-5). The BNT score from baseline to three days in the neurotomy plus intensive SLT group was higher than in the control group (group difference 5.08, 3.44 to 6.71, P<0.001). Treatment effects remained significantly stable at six months (group difference 8.26, 4.16 to 12.35, P<0.001) (table 2, fig 2, and supplementary table S2). The sensitivity analysis of the primary efficacy outcome with mixed effect model also favoured the neurotomy and intensive SLT group in increase of BNT score from baseline to each follow-up visit (see supplementary table S3). Predefined and post hoc subgroup analyses showed similar differences between subgroups for type of stroke, type of aphasia, hemiparesis, severity of aphasia, duration of disease, or other listed personal factors (see supplementary figure S3).

Secondary outcomes

Compared with the control group, the neurotomy and intensive SLT group showed increases in total aphasia quotient from baseline to three days (group difference 5.82, 95% CI 4.00 to 7.64, P<0.001) and in three out of four subsets of the western aphasia battery—spontaneous speech, comprehension, and naming (table 2). At one month, changes in total aphasia quotient favoured the neurotomy and intensive SLT group (group difference 7.06, 4.41 to 9.72, P<0.001) and all four subsets of the western aphasia battery. The total western aphasia battery score remained mainly stable at six months (see supplementary figure S4). No significant difference was found in physiological or structural changes relating to voice function in either group as evaluated by the international classification of functioning, disability, and health score (see supplementary figure S5).

For patient reported outcomes, the mean change in activities of daily living measured using the Barthel index from baseline to one month was 3.00 points in the neurotomy and intensive SLT group compared with −1.20 points in the control group (group difference 4.12, 95% CI 0.23 to 8.00, P=0.04) (table 2 and supplementary figure S6). The mean group difference in Barthel index scores at three days and six months was −1.28 (95% CI −3.95 to 1.39) and 3.93 (0.38

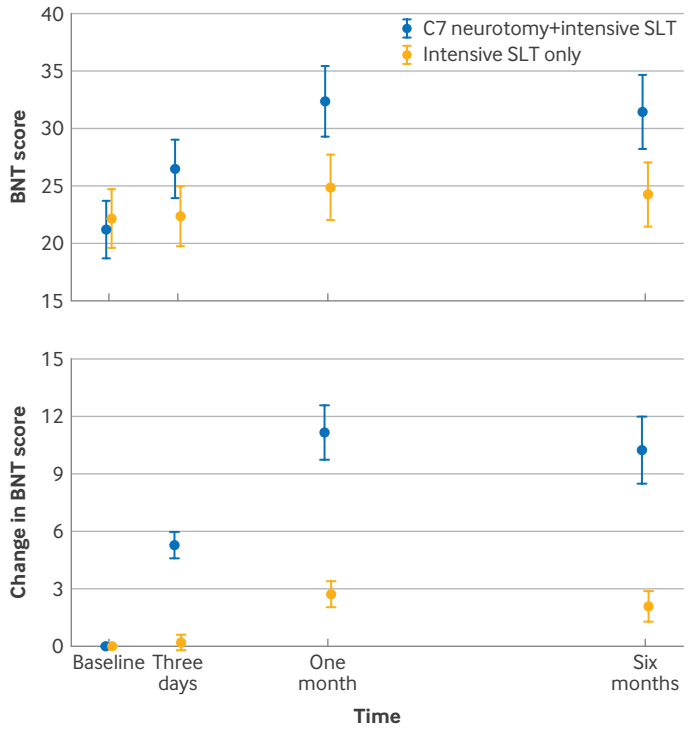

Fig 2 | Mean change in BNT score (standard error) from baseline in C7 neurotomy plus intensive SLT group and intensive SLT only group. Data are from baseline to three days after surgery in the neurotomy plus intensive SLT group or three days after start of one week's deferral of intensive SLT in the control group, one month from surgery or start of deferral, and baseline to six months after start of intensive SLT. BNT=Boston naming test; C7 neurotomy=right neurotomy of the seventh cervical nerve at the intervertebral foramen; SLT=speech and language therapy

to 7.49), respectively. For post-stroke depression measured using the stroke aphasic depression questionnaire-hospital version, the mean decrease from baseline to six months was 1.64 points in the neurotomy and intensive SLT group and 0.43 in the control group (group difference −1.28, 95% CI −2.01 to −0.54, P=0.001) (table 2 and supplementary figure S7). The mean group difference at three days and one month was 0.55 (−0.37 to 1.46, P=0.24) and −0.60 (95% CI −1.66 to 0.47, P=0.27), respectively.

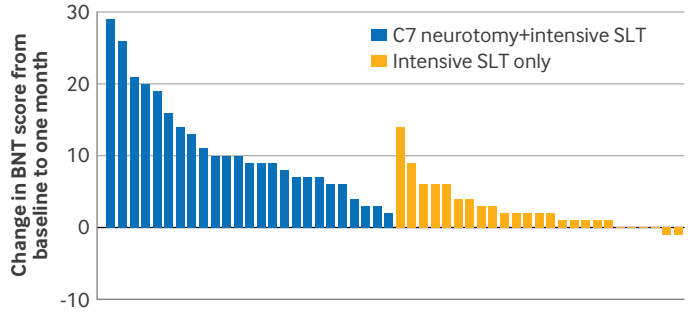

Fig 3 | Waterfall plot depicting observed change in BNT score for each participant from baseline to one month follow-up in C7 neurotomy plus intensive SLT group and intensive SLT only group. BNT=Boston naming test; C7 neurotomy=right neurotomy of the seventh cervical nerve at the intervertebral foramen; SLT=speech and language therapy

Functional MRI

To elucidate the roles for language processing of detected regions, we used the dual stream model proposed by Hickok and Poeppel[28-30] (top images in figure 4 show the ventral and dorsal pathways). For the neurotomy and intensive SLT group, correlation between BNT score and brain activation during overt picture naming was primarily seen in the right hemisphere, including right supramarginal gyrus at both one month and six months after surgery, right inferior frontal gyrus at one month, and left inferior temporal gyrus at six months (fig 4 and supplementary table S6). In the intensive SLT only group, however, such correlation was shown mostly in the left hemisphere, including left precentral gyrus, left fusiform gyrus, and right lingual gyrus at one month, and left precentral gyrus and middle frontal gyrus at six months (see supplementary table S7 and figure S8).

Safety outcomes

No severe treatment related adverse events were reported. Adverse events that were related to C7 neurotomy included decreased sensory and motor function, neuropathic pain in the right upper arm or shoulder, and increased blood pressure. Fifteen patients in the neurotomy and intensive SLT group reported neuropathic pain and used analgesics (table 3). Beyond conventional recording of the onset and severity of neuropathic pain, we also collected data on the use of analgesics in patients with neuropathic pain after surgery. Among 25 patients in the neurotomy and intensive SLT group, 15 (60%) used analgesics for a median duration of 32 days (range 14-60 days)—that is, neuropathic pain improved within two months after surgery, and no patient needed long term treatment with analgesics (see supplementary table S8). At the six month follow-up, participants no longer experienced the neurotomy related adverse events (table 3). The recorded adverse events in sensorimotor function agreed with those in a previous study.[9 10]

Discussion

In this multicentre randomised controlled trial, right neurotomy of the seventh cervical nerve at the intervertebral foramen plus three weeks of intensive SLT significantly improved language function, especially naming ability, in patients with chronic aphasia due to left hemispheric stroke, compared with patients who received three weeks of intensive SLT only. The increase in language function remained stable at six months' follow-up. Additionally, the aphasia quotient, patient reported quality of life, and relative or care giver reported post-stroke depression also improved in the neurotomy plus intensive SLT group. No significant difference was found in the subgroup analysis for moderators of treatment effect (sex, age, duration of disease, type of stroke, type of aphasia, severity of aphasia, and centres), indicating that no particular feature of patient subgroups was driving the effect. Functional MRI scanning after the intervention provided important evidence for plasticity of the right

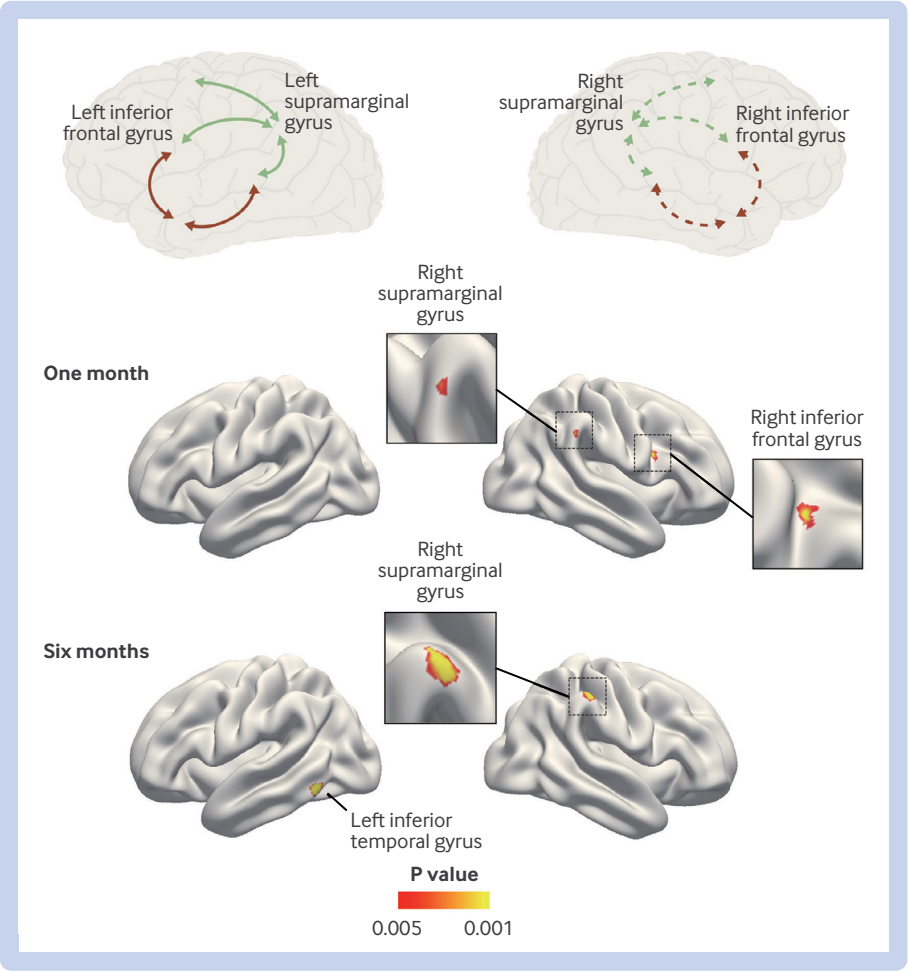

Fig 4 | Dynamic changes in correlation map between BNT score and brain activation during overt picture naming in C7 neurotomy plus intensive SLT group. Top images are schematic of proposed bilateral pathway for language processing based on dual stream model by Hickok and Poeppel.[28-30] The dorsal stream (green) projects from superior temporal gyrus towards supramarginal gyrus, inferior frontal gyrus, and regions in motor pathways, whereas the ventral stream (brown) projects towards anterior middle and inferior temporal gyrus and inferior front gyrus. The BNT score in the neurotomy plus intensive SLT group correlated with brain activation in right supramarginal gyrus and right inferior frontal gyrus at one month, and with right supramarginal gyrus and left inferior temporal gyrus at six months. No significant cluster was observed at baseline in either group. The probability threshold for all images was set at P<0.005 and cluster corrected at P<0.05. BNT=Boston naming test; C7 neurotomy=neurotomy of the seventh cervical nerve at the intervertebral foramen; SLT=speech and language therapy

hemisphere during the overt naming task, which indicated that transection of the peripheral nerve could induce large plasticity in language processing and activate spared areas in the right hemisphere.

Comparison with other studies

Chronic aphasia after stroke is a major challenge. Although many aspects of language function can be affected, disability in naming function is one of the most difficult to improve. BNT is a common index to evaluate naming function. Intensive SLT has been widely used as a routine and accessible treatment for chronic aphasia after stroke. The percentage improvement in naming score was not, however, uniform in the study. From literature review, the total amount or intensity of SLT, duration of aphasia, and patients' functional reserve at baseline are all potential factors that affect the final outcomes.[4 31] In a systematic review, the mean increase in BNT score after intensive SLT of more than four hours weekly was between 2.87 points (4.8%) and 5.71 points (9.5%), depending on the total amount of treatment each week.[24] Besides intensive SLT, different new treatments have been tried, including implanted or non-invasive transcranial brain stimulation, computer based rehabilitation, and motor language therapy.[32-35] A study in 2012 found that implanted epidural cortical stimulation and aphasia therapy for six weeks improved BNT score by 8.25 points (13.8%),[32] whereas a study in 2021 found a mean increase of 6.7 points (11.7%) after non-invasive intermittent theta burst stimulation for three weeks.[34]

In this study, we reported a new treatment, C7 neurotomy plus intensive SLT, and validated its effectiveness. The improvement in BNT score was

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Table 3 | Adverse events in participants with chronic aphasia after stroke assigned to receive C7 neurotomy plus intensive SLT or intensive SLT alone

	C7 neurotomy+intensive SLT (n=25)			Intensive SLT (n=25)		
Adverse events	Three days	One month	Six months	Three days	One month	Six months
Unrelated to treatment	2	15	0	0	12	0
Treatment related	49	63	0	0	3	0
Neurotomy related in patients with arm spasticity (n=21):						
Decreased sensory function*	21	20	0	-	-	-
Decreased motor function†	19	18	0	-	-	-
Neuropathic pain (or numbness)	2	9	0	-	-	-
Increased blood pressure	0	2	0	0	0	0
Neurotomy related in patients without spasticity (n=4):						
Decreased sensory function*	4	4	0	-	-	-
Decreased motor function†	3	2	0	-	-	-
Neuropathic pain	0	4	0	-	-	-
Increased blood pressure	0	2	0	0	0	0
Other treatment related:						
Increased blood glucose level	0	0	0	0	2	0
Temporal sleep disorder	0	0	0	0	1	0
Haematoma	0	1	0	0	0	0
Thrombus‡	0	1	0	0	0	0

C7 neurotomy=right neurotomy of the seventh cervical nerve at the intervertebral foramen; SLT=speech and language therapy.
*Change in sensation (from sensitive to insensitive) was considered a decrease in sensory function. This was evaluated in the thumb, index finger, and middle finger.
†Any decrease in motor function was recorded, with assessments focusing on extension of the elbow, wrist, and finger.
‡One patient had venous thrombosis of leg due to a previous thrombosis filter not being removed. This patient recovered fully 10 days later without any effect on motor or sensory function.

11.16 points (18.6%) at one month after neurotomy plus intensive SLT, compared with 2.72 points (4.5%) after intensive SLT only. Treatment effects were evident at three days after surgery, before the initiation of intensive SLT, and remained stable at six months' follow-up. Therefore, this study proposes a new and effective treatment for chronic aphasia after stroke. Although C7 neurotomy is a surgical intervention, it did not result in any additional severe adverse events or lasting troublesome symptoms. From the timing of each follow-up point, it could be concluded that surgery contributed to about half of the increase in language function and intensive SLT for three weeks to the other half, and most of the gains in language function were maintained during six months of follow-up. As a comparison, patients in the control group who only received three weeks of intensive SLT showed significantly less improvements in language function. This suggests that C7 neurotomy can not only improve language function directly but also promote the effects of intensive SLT. As improvement started as early as the first postoperative day in most patients, it could be speculated that neurotomy of the seventh cervical nerve triggered changes in plasticity of the brain regions responsible for language.

C7 neurotomy could rapidly improve spasticity of the right arm. Could this decrease of spasticity play a role in improving language function in patients with aphasia? We did a subgroup analysis to compare the improvements in BNT score between 21 patients with spastic arm paralysis and four patients without spastic arm paralysis in the neurotomy plus intensive SLT group and found no significant interaction effect. Although the number of patients without spastic arm paralysis was relatively small, leading to a wide confidence interval and diminished power, it at least indicated that release of spasticity was not the major reason for improvements in language function.

To elucidate the role of brain plasticity in the improvement of naming ability, we obtained three functional MRI scans, at baseline and at one month and six months after surgery. In the neurotomy plus intensive SLT group, BNT score correlated with brain activation in the right supramarginal gyrus and right inferior frontal gyrus at one month, and with right supramarginal gyrus and left inferior temporal gyrus at six months. The compensatory role of the right supramarginal gyrus, corresponding to Wernicke's area of the left hemisphere, for aphasia has been reported previously.[36 37] Left inferior temporal gyrus and right inferior frontal gyrus also showed activation during recovery. Since the patients' language function improved within three days after C7 neurotomy, we believe that brain plasticity also occurs immediately after surgery. Therefore, C7 neurotomy induced plasticity seems to be a dynamic process[36 38-40] (fig 4). Further experiments of day-by-day observations are still needed to validate the dynamic plasticity process from immediately after surgery to the plateau period of more than one year. A previous study[9] found that rewiring the C7 nerves of patients with spastic hand after stroke resulted in regained function of neuroplasticity in the uninjured sensorimotor area. The related editorial commented that "This is creative use and represents a fresh approach."[41] In another study, right C7 nerve root neurotomy led to rapid and massive changes in the right dorsal ganglion,[42] an extension of the central sensorimotor area. In this study, C7 neurotomy induced neuroplasticity in the uninjured area to regain function in patients with aphasia after stroke. Integrating these results, we can assume that "rewiring of the peripheral nervous system, harnessed neuroplasticity, and

restored central nervous system"[43] can be expanded beyond sensorimotor disorders alone.

Strengths and limitations of this study

A strength of this trial was its rigorous design as we proposed a new treatment for chronic aphasia after left hemispheric stroke—right C7 neurotomy at the intervertebral foramen combined with intensive SLT. Besides evaluating language function, we also provided data on quality of life from patient self-report and depression after stroke from a close relative or care giver, which showed significant improvements six months after surgery. This study also provides important evidence for changes in the brain using functional MRI scanning after intervention, which indicated that peripheral nerve transection could induce large plasticity in the language network and activate spared areas in the right hemisphere.[5 13 35]

The main limitation of this study was the inclusion of only native Chinese speakers, who were all recruited from the east coast of mainland China. An international multicentre trial recruiting participants who speak other languages would be important in further studies. Although the criteria for eligibility to take part in the study covered more than 60% of the overall numbers of patients with aphasia after stroke and did not set restrictions on sex or type of stroke, the participants were relatively young and mostly men with a higher percentage of haemorrhagic stroke compared with the overall population of stroke. Although follow-up for six months is considered long enough for language function, an extended follow-up study is still needed to verify patients' performance over a longer time scale. Therefore, we plan to observe the patients in this study for five years to evaluate their language performance. Functional MRI in this study revealed dynamic patterns of brain plasticity, but follow-up at different time points and additional detection methods are still needed to further explore the underlying mechanisms.

Conclusions

Right C7 neurotomy at the intervertebral foramen plus intensive SLT is a superior treatment for chronic aphasia after stroke compared with intensive SLT alone. Moreover, patients in the neurotomy plus intensive SLT group showed improvements in quality of life and depression after stroke. Therefore, neurotomy plus intensive SLT could be considered an evidence based intervention for patients aged 40-65 years with aphasia for more than one year after stroke.

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Ethical approval: The trial protocol was approved by the institutional review boards of all the trial centres, and all participants provided written informed consent.

Data sharing: All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted after review. Data will be shared, with investigator support, after approval of a proposal and signed data access agreement.

Transparency: The lead author (FJT) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results of this study will be communicated to patients who expressed an interest during their clinic visits, and also disseminated through press releases, academic conferences, and social media.

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Video 1: Surgical procedure for C7 neurotomy at intervertebral foramen (also see supplementary videos S2-S5 showing changes in language function of typical patients from each study arm during six months' follow-up)
fenj083613-vid1The BMJ Video Player

Supplementary information: Additional material
Video 1: C7 neurotomy procedure
Videos 2-4: Each video shows changes in language function in three typical patients in C7 neurotomy plus intensive speech and language therapy (SLT) group at six months' follow-up
Video 5: Changes in language function in three typical patients in intensive SLT only group at six months' follow-up