HHS Public Access

Author manuscript

Int J Stroke. Author manuscript; available in PMC 2022 December 01.

Published in final edited form as:

Int J Stroke. ; : 17474930211017807. doi:10.1177/17474930211017807.

Treatment of Post-Stroke Aphasia: A Narrative Review for Stroke Neurologists

Emilia Vitti, **Argye E. Hillis**

Johns Hopkins University School of Medicine, Department of Neurology

Abstract

This review is intended to help physicians guide patients to optimal management of post-stroke aphasia. We review literature on post-stroke aphasia treatment, focusing on: (1) when and for whom language therapy is most effective, (2) the variety of approaches that can be effective for different individuals, and (3) the extent to which behavioral therapy might be augmented by non-invasive brain stimulation and/or medications.

Introduction

Every stroke neurologist is familiar with aphasia. It occurs in about one third of stroke patients, most often in those with left cortical stroke[1]. It has a profound effect on quality of life after stroke[2]. There have been many recent reviews of its treatment[3], but this one is aimed at providing helpful information to stroke clinicians, particularly neurologists. We will not provide details regarding interventions, as these are typically determined by a speech-language pathologist, on the basis of the individual's needs, goals, and profile of performance on language tests. Rather, here we provide a review of evidence regarding: (1) when and for whom language therapy is most effective, (2) the variety of approaches that can be effective for different individuals, and (3) the extent to which behavioral therapy might be augmented by non-invasive brain stimulation and/or medications. We begin by discussing approaches to behavioral therapy, because medications and non-invasive brain stimulation have been used to boost the effects of behavioral interventions, rather than used independently. Our aim is to provide a practical overview that will guide physicians in deciding who, when, and where to refer people with aphasia. It addresses common problems faced by physicians when caring for patients with post-stroke aphasia.

There have also been recent reviews of the mechanisms underlying interventions to improve language after stroke,[4] that have been revealed by changes in activation or functional or structural connectivity in language networks in functional imaging of language before and after treatment[4,5]. Here we focus on empirical evidence of treatment effects, and refer the interested reader those reviews of mechanisms.

Corresponding author: Argye E. Hillis, Department of Neurology, 600 N. Wolfe Street, Phipps 446, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA, argye@jhmi.edu.

Declaration of Interest: The authors have no conflicts of interest to disclose.

BEHAVIORAL INTERVENTIONS: SPEECH AND LANGUAGE THERAPY (SLT)

Two main, complementary approaches to intervention are impairment-based approaches and functional communication approaches. These types of treatments can appropriately be undertaken simultaneously or at different time periods for the same patient, or used at the same time post-stroke with patients with different profiles of impairment. *Impairment based approaches* aim to improve specific language processes, such as lexical-semantics, phonology, or syntax[6], or performance on specific language tasks, such as naming, reading, spelling, or word and sentence comprehension[7]. *Functional communication approaches* emphasize helping the individual communicate in every day circumstances, by eliminating communication barriers in the environment, improving success of communication by any modality (gestures, drawing, pointing, etc.) and caregiver training to enhance communication (see Martin, et al.[8] for illustrations of the two approaches to the same problem). Impairment-based approaches are likely effective by inducing reorganization of structure-function relationships in the brain; i.e. by inducing unimpaired brain regions to assume the function of the damaged regions[9]. Functional communication approaches are compensatory; i.e. aimed to allow the individual to compensate for deficits to reduce language disability.

Efficacy of SLT

Numerous single-subject studies with multiple baseline or cross-over design and small group studies (e.g.,[10]) demonstrate the effectiveness of a particular therapy for one or more individuals with a particular deficit. These studies are essential because language is complex, and no one therapy is useful for all deficits. Meta-analyses of these small studies generally show a statistically significant positive effect[11,12]. The very few studies comparing the effectiveness of different types of therapy for the same individuals have been small and inclusive, although a relatively large (n=100) cross-over trial with randomized order of a semantic versus phonological treatments has recently been completed and results are forthcoming[13]. Importantly, a recent large Phase III randomized controlled trial showed that a structured SLT improves speech production and communication quality of life in chronic aphasia[14].

Timing of SLT

No study has directly compared effects of a specific language therapy provided at the acute or subacute stage versus the chronic stage after stroke. Animal models of stroke indicate impairment-based therapy should take advantage of the neuroplasticity that is highest early after stroke[15]. Indeed, SLT is most commonly provided in the acute or subacute time period, and seems to be effective[16]. However, as most patients improve in the first three months after stroke irrespective of intervention (but see[17]), it is very difficult to show a significant effect over and above the spontaneous recovery[18]. However, carefully controlled studies of interventions more targeted to the individual's particular deficits in the early stages after stroke clearly demonstrate positive effects[19].

Even though SLT is most commonly provided early after stroke, the strongest evidence for treatment efficacy is in chronic aphasia[20]. Reduction in language impairment with

structured SLT in chronic aphasia has been demonstrated through Phase III randomized clinical trials[14]. In fact, more SLT sessions in the chronic phase, even many years after stroke, is associated with greater recovery[21]. About 50% of chronic stroke patients continue to improve in language even decades after stroke, even though motor recovery may have plateaued earlier[22], and additional SLT facilitates recovery.

Amount of SLT

Although there is insufficient evidence to recommend an optimal dose of SLT[23], the therapist ideally determines the optimal number and duration of treatment sessions for each individual. Unfortunately, the number of sessions received may be limited by third-party payers or other practicalities (e.g. transportation). Studies show that more SLT leads to more gains,[24] but most patients receive only about 15 sessions[25]. Aphasia Centers[26], telerehabilitation[27], self-administered computerized SLT[28–30] can increase the amount and efficacy of therapy. For example, a large controlled trial (N=278) randomized patients with chronic aphasia to: (1) usual care; (2) usual care plus self-administered computerized SLT; or (3) usual care plus attention therapy. The greatest improvement in naming ($p<0.0001$) was seen in those who received the computerized SLT[26].

Type of Therapy

Physicians do not typically order a specific type of SLT. Nevertheless, it is important to know a wide range of SLT approaches are provided, so that lack of success with one approach may not indicate that the patient has “plateaued” in language recovery. For example, for patients with apraxia of speech, a number of structured treatments have been shown to be effective, including Speech Entrainment, in which the clinician and patient read aloud a passage simultaneously, with both visual and auditory mirroring[31]. Other effective approaches to treatment of apraxia of speech and/or language deficits include Oral Reading for Language in Aphasia, Melodic Intonation Therapy, Speech Production Treatment, Phonomotor Treatment, Response and Elaboration Treatment (see[30], for a comprehensive review). For patients with lexical-semantic deficits that underlie impaired naming and/or comprehension, both Semantic Feature Analysis[32] and a computerized treatment of word-picture verification have been shown to be effective[33]. Also, several studies have demonstrated gains in in grammatical processing, in both speech production and comprehension, using a structured therapy targeted to grammatical processing, in patients with Broca’s aphasia[34]. A very different approach, designed for people with aphasia with a wider range of language deficits, is constraint-induced aphasia therapy (CIAT)[35]. Patients are encouraged to communicate only with speech, and discouraged from using other modalities, such as pointing, drawing, gestures, or writing, to communicate. Several trials have shown that this approach can improve speech production,[36] although no more than usual care SLT provided at similar intensity levels[37,38]. An older, but widely used and effective treatment that encourages the use of both speech and other forms of communication (gestures, drawing, pointing) to communicate a concept is Promoting Aphasic’s Communicative Effectiveness (PACE[39], Davis, 2005). In PACE, the patient is asked to communicate information depicted in a picture that is not seen by the clinician. In alternate trials, the clinician communicates information in picture not seen by the patient, modeling various methods to communicate. Life Participation Approaches to Aphasia

(LPAA), like PACE, takes almost the opposite approach to CIAT. LPAA focuses on encouraging people with aphasia to use residual personal strengths to communicate in any modality that is effective, and will ultimately allow the person to reintegration into the community[32]. Often individualized strategies for effective communication are identified and then practiced by aphasic patient and their communication partners[40]. Another advancement in aphasia treatment has been the development of: (1) Aphasia Groups[41], which may be in-person or remote using telecommunication and include social communication activities such as book clubs, (2) Intensive Comprehensive Aphasia Program (ICAPs;[32]) that provide intensive, daily treatment sessions using a variety of behavioral approaches tailored to a small group of patients over 2–4 weeks in a camp-like setting, and (3) Aphasia Centers[42] that provide the individual with a variety of experiences in communication over a longer period, which have psycho-social benefits as well as gains in communication and various aspects of language[43]. Because several large RCTs provide evidence that patients with chronic, severe aphasia are unlikely to respond to impairment-based therapy[14,18,44] these patients are likely to benefit most from compensatory approaches, including training communication partners[45], alternative communication modalities[46], or use of augmentative communication devices[47].

PHARMACEUTICAL INTERVENTIONS

Acute Interventions

In acute ischemic stroke, the primary mechanism of recovery is restoration of blood flow to the penumbral tissue surrounding the core infarct. Numerous large randomized controlled trials (RCTs) have shown overall benefit in outcome with intravenous thrombolysis[48] or endovascular therapy[49]. While these trials have not been designed to evaluate the effects on language, a secondary analysis of a large RCT of endovascular therapy (MR CLEAN) showed greater in the language score (0–2 points) on the NIH Stroke Scale in the intervention group compared to the control group[50]. Furthermore, case series have shown that such interventions can result in improvement of language functions[51]. One small RCT also showed that temporary elevation of blood flow to improve perfusion early after left hemisphere stroke due to large vessel occlusion or stenosis was associated with language improvement[52].

Chronic Interventions

In chronic post-stroke aphasia, no RCT has yet provided evidence that pharmaceutical intervention, in the absence of SLT, results in significant improvement in language[53]. However, several trials have shown that some medications may augment the effects of SLT. A plausible mechanism of the augmentation effects of medications that modulate neurotransmitters is that language recovery often depends on neuroplasticity. That is, neural networks supporting language can be modified by: (1) incorporating new nodes into the network or (2) changing connectivity between undamaged nodes of the residual language network. Alternatively, other networks might be engaged to assume the functions of the damaged networks[54,55]. Evidence from both humans and animals indicate that behavioral interventions such as mass practice can lead to this type of reorganization, through short- or long-term neural plasticity, facilitated by the availability of neurotransmitters such as

acetylcholine, norepinephrine, serotonin, and dopamine[56,57]. Therefore, medications that enhance the availability of these neurotransmitters could increase neuroplasticity[58]. Most trials of medications to augment recovery have studied motor recovery, but several RCTs have evaluated their effects on post-stroke language recovery.

Early RCTs evaluated the effects of sympathomimetics, which elevate brain catecholamines. A few small nonrandomized trials (see Llano and Small[59]) and one larger RCT[60] demonstrated small, but statistically significant effects of dextroamphetamine in augmenting language therapy to improve language test scores. However, results were not adjusted for differences in language therapy duration and have not been subsequently replicated. One RCT that combined levodopa with language therapy showed statistically significant effects of levodopa on a subset of language tasks[61]. However, a small (N=10) prospective, placebo-controlled, double-blind crossover study with randomized order of therapy in patients with chronic post-stroke aphasia showed no effect of levodopa, although intensive language therapy resulted in significant and durable gains in language[62]. Likewise, a RCT of bromocriptine (without SLT) showed no benefit over placebo on language performance[63].

Cholinesterase inhibitors have been evaluated in small, uncontrolled studies and two RCTs for aphasia recovery. A RCT of 26 patients with chronic post-stroke aphasia showed greater improvement in aphasia severity at the end of 16 weeks of therapy with donepezil (10 mg/day) relative to placebo ($p=0.037$)[64]. However, group differences did not persist after the four-week wash-out period. A larger RCT of 60 patients with post-stroke aphasia, showed higher language scores with donepezil versus placebo, and the difference persisted after the four-week wash out ($p<0.01$), but the effect size was very small[65].

Memantine, a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, with effects on serotonin and dopamine receptors and potential reduced excitotoxicity[66], has shown similar small positive effects, possibly due to positive effects on more general cognitive functions such as attention or memory. A RCT of memantine plus SLT showed significantly greater improvements with both interventions compared to placebo or memantine alone after 16 weeks of therapy (gains of 8.5±0.9 vs. 3.5±0.8 on a 100 point score; $p=0.00001$), which declined but remained significant after a four-week washout period (6.0±0.8 vs. 3.9±0.8 on a 100 point score; $p=0.041$)[67]. However, the small group differences (2.1 to 5 points on a 100-point summary score), might not have functional significance, and the trial was not blinded. A more recent study showed that both memantine and SLT were associated with changes in cortical activity (measured with ERP) that correlated with language gains[68].

Selective serotonin reuptake inhibitors (SSRIs), which have been shown to have a positive effect on post-stroke motor recovery measured with the Fugl Meyer scale[69] and greater improvements on a cognitive battery[70], but no effect on the less sensitive modified Rankin Scale[71,72] have not been studied in RCT for aphasia recovery. However, a RCT of escitalopram plus language therapy vs. placebo plus language therapy in subacute post-stroke aphasia is underway (NCT03843463).

NONINVASIVE BRAIN STIMULATION

Non-invasive brain stimulation, such as repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS), is a promising alternative approach to enhancing neuroplasticity to augment language recovery. rTMS, which modulates neural activity by reducing (inhibitory, low rate rTMS) or increasing (excitatory or high rate rTMS) synaptic firing can be used with or without SLT. In contrast, tDCS only changes the threshold of activation of neurons in the network activated by the concurrent behavioral task, such as SLT. The current is not strong enough to generate action potentials alone, so it is only effective for language improvement when used concurrently with SLT[73]. Anodal (excitatory) tDCS reduces the threshold of activation of the network stimulated by the ongoing task, while cathodal tDCS has mixed effects[73], but mostly inhibitory, by increasing the threshold of activiation[74]. Both animal and human studies have yielded evidence that the effects of tDCS depend on a Brain Derived Neurotrophic Factor-dependent mechanism[75]. Although tDCS has fairly widespread effects on neural activity, one functional MRI study showed that the effects are specific to the entire network activated by the concurrent behavioral task, as long as tDCS is applied to any part of the network[76].

Trials of tDCS

One advantage of tDCS over TMS is that an excellent sham control is possible; participants are unable to distinguish the sham from real tDCS. In the sham condition, 1–4 mA stimulation is applied for 30 seconds, but then faded gradually to 0 mA, which mimics the sensation of continuous (e.g. 20 minutes) 1–4 mA stimulation, in which stimulation is generally perceived for only the first 20–30 seconds[73]. Most recent RCTs have evaluated the effects of 1–2 mA of anodal or cathodal tDCS, applied for 15–20 minutes. This "dose" is based on studies by Fritsch et al.[75] showing that 15 minutes of continuous tDCS significantly increases BDNF levels for more than one hour. More than 35 RCTs of post-stroke aphasia, using anodal (usually applied to left hemisphere) or cathodal tDCS (usually applied to right hemisphere), or both have been published (see a systematic review[77]). Most of these trials in chronic post-stroke aphasia, including the largest (N=74) double-blind RCT of tDCS[78], have reported significantly greater improvement in the primary outcome measure (generally a language task) relative to the sham group or condition[79]. Most of the negative trials have studied tDCS in few (5 or fewer) therapy sessions[80]. Only a couple of studies have been conducted in subacute stroke, but those that included greater than 5 therapy sessions have been positive, and others are ongoing (e.g. NCT02674490).

Trials of rTMS

Although most RCTs include a sham group or condition, the conditions are generally distinguishable when participants receive both conditions. Thus, randomized parallel group, rather than crossover trials are preferred (but see Rubi-Fessen et al.[81]). Most trials of low frequency or high frequency rTMS in subacute stroke have reported significantly greater language improvement in the rTMS than in the sham group or condition,[82] sometimes lasting for at least 3 months[83]. Similar positive effects of rTMS have been reported in chronic post-stroke aphasia (see meta-analysis[84]). Table 1 summarizes the results of recent trials of SLT and noninvasive brain stimulation with more than 20 participants.

CONCLUSIONS

Behavioral SLT remains the standard of care post-stroke aphasia, although different approaches to SLT may be more appropriate at different times after stroke, or for patients with different levels of severity. Most studies indicate that more time in therapy is more effective, and time in therapy may be enhanced by telerehabilitation, self-administered therapy (e.g., through language therapy apps), or participation in aphasia groups, intensive comprehensive aphasia programs, or Aphasia Centers. Alternatively or additionally, relatively small trials suggest that the efficiency and effectiveness of aphasia therapy might be enhanced by medications or non-invasive brain stimulation in addition to SLT. It is important for referring physicians to be aware that SLT can be effective regardless of the time post-stroke, and to refer patients or families to databases of ongoing clinical trials, such as ClinicalTrials.gov. Participation in clinical trials can benefit not only the scientific community (by evaluating the effects of interventions), but also the participants, who are likely to receive some sort of SLT without monetary cost. Because aphasia is associated poor quality of life, even worse, on average, than conditions such as dementia or cancer[2], patients with post-stroke aphasia deserve an opportunity for rehabilitation regardless of the time post-stroke or severity.

Acknowledgements

The authors were supported by funding from NIH (NIDCD) through P50DC014664 and R01DC05375.

References

1. Flowers HL, Skoretz SA, Silver FL, et al. Poststroke aphasia frequency, recovery, and outcomes: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2016;97(12):2188–2201. [PubMed: 27063364]
2. Lam JMC, Wodchis WP. The relationship of 60 disease diagnoses and 15 conditions to preference-based health-related quality of life in Ontario hospital-based long-term care residents. Med Care. Published online 2010:380–387. [PubMed: 20220536]
3. Berube S, Hillis AE. Advances and innovations in aphasia treatment trials. Stroke. 2019;50(10):2977–2984. [PubMed: 31510904]
4. Fridriksson J, Smith K. Neuroplasticity associated with treated aphasia recovery. In: Neurobiology of Language. Elsevier; 2016:1007–1013.
5. Kiran S, Meier EL, Johnson JP. Neuroplasticity in aphasia: A proposed framework of language recovery. J Speech, Lang Hear Res. 2019;62(11):3973–3985. [PubMed: 31756154]
6. Edmonds LA, Mammino K, Ojeda J. Effect of verb network strengthening treatment (VNeST) in persons with aphasia: Extension and replication of previous findings. Am J Speech-Language Pathol. 2014;23(2):S312–S329.
7. Hillis AE. The Handbook of Adult Language Disorders. Psychology Press; 2015.
8. Martin N, Thompson CK, Worrall L. Aphasia Rehabilitation: The Impairment and Its Consequences. Plural Publishing; 2007.
9. Hillis AE. For a theory of rehabilitation: progress in the decade of the brain. Eff Rehabil Cogn deficits. Published online 2005:271–280.
10. Hillis AE. The role of models of language processing in rehabilitation of language impairments. Aphasiology. 1993;7(1). doi:10.1080/02687039308249497
11. Brady MC, Kelly H, Godwin J, Enderby P, Campbell P. Speech and language therapy for aphasia following stroke. Cochrane database Syst Rev. 2016; (6).

12. Robey RR. A meta-analysis of clinical outcomes in the treatment of aphasia. J Speech, Lang Hear Res. 1998;41(1):172–187. [PubMed: 9493743]
13. Spell LA, Richardson JD, Basilakos A, et al. Developing, Implementing, and Improving Assessment and Treatment Fidelity in Clinical Aphasia Research. Am J speech-language Pathol. 2020;29(1):286–298.
14. Breitenstein C, Grewe T, Flöel A, et al. Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. Lancet. 2017;389(10078):1528–1538. [PubMed: 28256356]
15. de Courten-Myers GM, Kleinholz M, Wagner KR, Xi G, Myers RE. Efficacious experimental stroke treatment with high-dose methylprednisolone. Stroke. 1994;25(2):487–492. [PubMed: 8303761]
16. Warren RL, Gabriel C, Johnston A, Gaddie A. Efficacy during acute rehabilitation. Clin aphasiology. 1987;17:1–11.
17. Hillis AE. The 'standard'for poststroke aphasia recovery. Published online 2010.
18. Godecke E, Armstrong E, Rai T, et al. A randomized control trial of intensive aphasia therapy after acute stroke: The Very Early Rehabilitation for SpEech (VERSE) study. Int J Stroke. Published online 2020:1747493020961926.
19. Hillis AE. Efficacy and generalization of treatment for aphasic naming errors. Arch Phys Med Rehabil. 1989;70(8):632–636. [PubMed: 2764694]
20. Kiran S, Fridriksson J, Bonilha L, Boyle M, Cherney LR, Dickey MW, Martin NRA. Disentangling aphasia treatment and spontaneous recovery in post-stroke aphasia recovery. Stroke.
21. Johnson L, Basilakos A, Yourganov G, et al. Progression of aphasia severity in the chronic stages of stroke. Am J speech-language Pathol. 2019;28(2):639–649.
22. Holland A, Fromm D, Forbes M, MacWhinney B. Long-term recovery in stroke accompanied by aphasia: A reconsideration. Aphasiology. 2017;31(2):152–165. [PubMed: 28713191]
23. Harvey S, Carragher M, Dickey MW, Pierce JE, Rose ML. Dose effects in behavioural treatment of post-stroke aphasia: a systematic review and meta-analysis. Disabil Rehabil. Published online 2020:1–12.
24. Carpenter J, Cherney LR. Increasing aphasia treatment intensity in an acute inpatient rehabilitation programme: a feasibility study. Aphasiology. 2016;30(5):542–565. [PubMed: 27026751]
25. Richard C, Katz B, Hallowell C, et al. A multinational comparison of aphasia management practices. Int J Lang Commun Disord. 2000;35(2):303–314. [PubMed: 10912257]
26. Hoover EL, Caplan DN, Waters GS, Carney A. Communication and quality of life outcomes from an interprofessional intensive, comprehensive, aphasia program (ICAP). Top Stroke Rehabil. 2017;24(2):82–90. [PubMed: 27456043]
27. Pitt R, Theodoros D, Hill AJ, Russell T. The impact of the telerehabilitation group aphasia intervention and networking programme on communication, participation, and quality of life in people with aphasia. Int J Speech Lang Pathol. 2019;21(5):513–523. [PubMed: 30200788]
28. Palmer R, Dimairo M, Cooper C, et al. Self-managed, computerised speech and language therapy for patients with chronic aphasia post-stroke compared with usual care or attention control (Big CACTUS): a multicentre, single-blinded, randomised controlled trial. Lancet Neurol. 2019;18(9):821–833. [PubMed: 31397288]
29. Fleming V, Brownsett S, Krason A, et al. Efficacy of spoken word comprehension therapy in patients with chronic aphasia: a cross-over randomised controlled trial with structural imaging. J Neurol Neurosurg Psychiatry. Published online 2020.
30. Stark BC, Warburton EA. Improved language in chronic aphasia after self-delivered iPad speech therapy. Neuropsychol Rehabil. 2018;28(5):818–831. [PubMed: 26926872]
31. Fridriksson J, Hubbard HI, Hudspeth SG, et al. Speech entrainment enables patients with Broca's aphasia to produce fluent speech. Brain. 2012;135(12):3815–3829. [PubMed: 23250889]
32. Cherney LR, Carpenter J. Handbook of Clinical Neurology. In: Hillis AE, Fridriksson J, eds. Handbook of Clinical Neurology. 3rd ed. Elsevier.
33. Fridriksson J, Baker JM, Whiteside J, et al. Treating visual speech perception to improve speech production in nonfluent aphasia. Stroke. 2009;40(3):853–858. [PubMed: 19164782]

34. Thompson C, Shapiro L. Treating agrammatic aphasia within a linguistic framework: Treatment of underlying forms. Aphasiology. 2005;19(10–11):1021–1036. [PubMed: 17410280]
35. Zhang J, Yu J, Bao Y, et al. Constraint-induced aphasia therapy in post-stroke aphasia rehabilitation: A systematic review and meta-analysis of randomized controlled trials. PLoS One. 2017;12(8):e0183349. [PubMed: 28846724]
36. Pulvermüller F, Neininger B, Elbert T, et al. Constraint-induced therapy of chronic aphasia after stroke. Stroke. 2001;32(7):1621–1626. [PubMed: 11441210]
37. Sickert A, Anders L-C, Münte TF, Sailer M. Constraint-induced aphasia therapy following sub-acute stroke: a single-blind, randomised clinical trial of a modified therapy schedule. J Neurol Neurosurg Psychiatry. 2014;85(1):51–55. [PubMed: 23828834]
38. Ciccone N, West D, Cream A, et al. Constraint-induced aphasia therapy (CIAT): a randomised controlled trial in very early stroke rehabilitation. Aphasiology. 2016;30(5):566–584.
39. Davis GA. PACE revisited. Aphasiology. 2005;19(1):21–38.
40. Kagan A, Simmons-Mackie N, Victor JC. The Impact of Exposure With No Training: Implications for Future Partner Training Research. J Speech, Lang Hear Res. 2018;61(9):2347–2352. [PubMed: 30208393]
41. Elman RJ. The importance of aphasia group treatment for rebuilding community and health. Top Lang Disord. 2007;27(4):300–308.
42. Simmons-Mackie N, Holland AL. Aphasia Centers in North America: A Survey. In: Seminars in Speech and Language. Vol 32. Thieme; 2011:203–215. [PubMed: 21968557]
43. Elman RJ. Aphasia centers and the life participation approach to aphasia. Top Lang Disord. 2016;36(2):154–167.
44. Nouwens F, de Lau LML, Visch-Brink EG, et al. Efficacy of early cognitive-linguistic treatment for aphasia due to stroke: a randomised controlled trial (Rotterdam Aphasia Therapy Study-3). Eur Stroke J. 2017;2(2):126–136. [PubMed: 29900407]
45. Holland AL. Pragmatic aspects of intervention in aphasia. J Neurolinguistics. 1991;6(2):197–211.
46. Purdie H, Baldwin S. Music therapy: challenging low self-esteem in people with a stroke. J Br Music Ther. 1994;8(2):19–24.
47. Nicholas M, Elliott S. C-Speak Aphasia: A communication system for adults with aphasia. Solana Beach, CA Mayer-Johnson Co. Published online 1998.
48. NINDS TPA. The National Institute of Neurological Disorders and Stroke RT-PA stroke study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333(24):1581–1587. [PubMed: 7477192]
49. Campbell BC V, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11):1009–1018. [PubMed: 25671797]
50. Crijnen YS, Nouwens F, de Lau LML, et al. Early effect of intra-arterial treatment in ischemic stroke on aphasia recovery in MR CLEAN. Neurology. 2016;86(22):2049–2055. [PubMed: 27170565]
51. Hillis AE. Pharmacological, surgical, and neurovascular interventions to augment acute aphasia recovery. Am J Phys Med Rehabil. 2007;86(6):426–434. [PubMed: 17515681]
52. Hillis AE, Ulatowski JA, Barker PB, et al. A pilot randomized trial of induced blood pressure elevation: Effects on function and focal perfusion in acute and subacute stroke. Cerebrovasc Dis. 2003;16(3). doi:10.1159/000071122
53. Berthier ML. Ten key reasons for continuing research on pharmacotherapy for post-stroke aphasia. Aphasiology. Published online 2020:1–35.
54. Crosson B, Rodriguez AD, Copland D, et al. Neuroplasticity and aphasia treatments: new approaches for an old problem. J Neurol Neurosurg Psychiatry. 2019;90(10):1147–1155. [PubMed: 31055282]
55. Stefaniak JD, Halai AD, Ralph MAL. The neural and neurocomputational bases of recovery from post-stroke aphasia. Nature. 2019;41582:19–282.
56. Brzosko Z, Mierau SB, Paulsen O. Neuromodulation of Spike-Timing-Dependent plasticity: past, present, and future. Neuron. 2019;103(4):563–581. [PubMed: 31437453]

57. Kirkwood A, Rozas C, Kirkwood J, Perez F, Bear MF. Modulation of long-term synaptic depression in visual cortex by acetylcholine and norepinephrine. J Neurosci. 1999;19(5):1599–1609. [PubMed: 10024347]
58. Kilgard MP, Merzenich MM. Cortical map reorganization enabled by nucleus basalis activity. Science (80-). 1998;279(5357):1714–1718.
59. Llano DA, Small SL. Pharmacotherapy for Aphasia. Neurobiol Lang. 2015; (December 2016):1067–1083. doi:10.1016/B978-0-12-407794-2.00085-7
60. Walker-Batson D, Curtis S, Natarajan R, et al. A double-blind, placebo-controlled study of the use of amphetamine in the treatment of aphasia. STROKE-DALLAS-. 2001;32(9):2093–2096.
61. Seniów J, Litwin M, Litwin T, Leśniak M, Członkowska A. New approach to the rehabilitation of post-stroke focal cognitive syndrome: effect of levodopa combined with speech and language therapy on functional recovery from aphasia. J Neurol Sci. 2009;283(1–2):214–218. [PubMed: 19268976]
62. Breitenstein C, Korsukewitz C, Baumgaertner A, et al. L-dopa does not add to the success of high-intensity language training in aphasia. Restor Neurol Neurosci. 2015;33(2):115–120. [PubMed: 25588456]
63. Ashtary F, Janghorbani M, Chitsaz A, Reisi M, Bahrami A. A randomized, double-blind trial of bromocriptine efficacy in nonfluent aphasia after stroke. Neurology. 2006;66(6):914–916. [PubMed: 16567711]
64. Berthier ML, Green C, Higueras C, Fernandez I, Hinojosa J, Martín MC. A randomized, placebo-controlled study of donepezil in poststroke aphasia. Neurology. 2006;67(9):1687–1689. [PubMed: 17101908]
65. Haixia YE, Shilin LI. A clinical randomized case-control study of donepezil in the treatment of aphasia after stroke. Chinese J Behav Med Brain Sci. 2014;23(3):225–227.
66. Lipton SA. Paradigm shift in neuroprotection by NMDA receptor blockade: memantine and beyond. Nat Rev Drug Discov. 2006;5(2):160–170. [PubMed: 16424917]
67. Berthier ML, Green C, Lara JP, et al. Memantine and constraint-induced aphasia therapy in chronic poststroke aphasia. Ann Neurol Off J Am Neurol Assoc Child Neurol Soc. 2009;65(5):577–585.
68. Barbancho MA, Berthier ML, Navas-Sánchez P, et al. Bilateral brain reorganization with memantine and constraint-induced aphasia therapy in chronic post-stroke aphasia: An ERP study. Brain Lang. 2015;145:1–10. [PubMed: 25932618]
69. Chollet F, Tardy J, Albucher J-F, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011;10(2):123–130. [PubMed: 21216670]
70. Jorge RE, Acion L, Moser D, Adams HP, Robinson RG. Escitalopram and enhancement of cognitive recovery following stroke. Arch Gen Psychiatry. 2010;67(2):187–196. [PubMed: 20124118]
71. Dennis M, Mead G, Forbes J, et al. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. Lancet. 2019;393(10168):265–274. [PubMed: 30528472]
72. Kraglund KL, Mortensen JK, Damsbo AG, et al. Neuroregeneration and vascular protection by citalopram in acute ischemic stroke (TALOS) a randomized controlled study. Stroke. 2018;49(11):2568–2576. [PubMed: 30355209]
73. Crinion J Transcranial direct current stimulation and aphasia therapy post stroke. Published online 2015.
74. Bindman LJ, Lippold OCJ, Redfearn JWT. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol. 1964;172(3):369. [PubMed: 14199369]
75. Fritsch B, Reis J, Martinowich K, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron. 2010;66(2):198–204. [PubMed: 20434997]
76. Holland R, Leff AP, Josephs O, et al. Speech facilitation by left inferior frontal cortex stimulation. Curr Biol. 2011;21(16):1403–1407. [PubMed: 21820308]

77. Biou E, Cassoudesalle H, Cogné M, et al. Transcranial direct current stimulation in post-stroke aphasia rehabilitation: A systematic review. Ann Phys Rehabil Med. 2019;62(2):104–121. [PubMed: 30660671]

78. Fridriksson J, Rorden C, Elm J, Sen S, George MS, Bonilha L. Transcranial direct current stimulation vs sham stimulation to treat aphasia after stroke: a randomized clinical trial. JAMA Neurol. 2018;75(12):1470–1476. [PubMed: 30128538]

79. Sebastian R, Kim JH, Brenowitz R, et al. Cerebellar neuromodulation improves naming in post-stroke aphasia. Brain Commun. Published online 2020.

80. Spielmann K, van de Sandt-Koenderman WME, Heijenbrok-Kal MH, Ribbers GM. Transcranial direct current stimulation does not improve language outcome in subacute poststroke aphasia. Stroke. 2018;49(4):1018–1020. [PubMed: 29523651]

81. Rubi-Fessen I, Hartmann A, Huber W, et al. Add-on effects of repetitive transcranial magnetic stimulation on subacute aphasia therapy: enhanced improvement of functional communication and basic linguistic skills. A randomized controlled study. Arch Phys Med Rehabil. 2015;96(11):1935–1944. [PubMed: 26189201]

82. Khedr EM, Abo El-Fetoh N, Ali AM, et al. Dual-hemisphere repetitive transcranial magnetic stimulation for rehabilitation of poststroke aphasia: a randomized, double-blind clinical trial. Neurorehabil Neural Repair. 2014;28(8):740–750. [PubMed: 24503205]

83. Tsai P-Y, Wang C-P, Ko JS, Chung Y-M, Chang Y-W, Wang J-X. The persistent and broadly modulating effect of inhibitory rTMS in nonfluent aphasic patients: a sham-controlled, double-blind study. Neurorehabil Neural Repair. 2014;28(8):779–787. [PubMed: 24526709]

84. Ren C-L, Zhang G-F, Xia N, et al. Effect of low-frequency rTMS on aphasia in stroke patients: a meta-analysis of randomized controlled trials. PLoS One. 2014;9(7):e102557. [PubMed: 25036386]

85. De Luca R, Aragona B, Leonardi S, et al. Computerized training in poststroke aphasia: what about the long-term effects? A randomized clinical trial. J Stroke Cerebrovasc Dis. 2018;27(8):2271–2276. [PubMed: 29880209]

86. Hilari K, Behn N, James K, et al. Supporting wellbeing through peer-befriending (SUPERB) for people with aphasia: A feasibility randomised controlled trial. Clin Rehabil. Published online 2021:0269215521995671.

87. Woodhead ZVJ, Kerry SJ, Aguilar OM, et al. Randomized trial of iReadMore word reading training and brain stimulation in central alexia. Brain. 2018;141(7):2127–2141. [PubMed: 29912350]

88. Fridriksson J, Elm J, Stark BC, et al. BDNF genotype and tDCS interaction in aphasia treatment. Brain Stimul. 2018;11(6):1276–1281. [PubMed: 30150003]

89. Meinzer M, Darkow R, Lindenberg R, Flöel A. Electrical stimulation of the motor cortex enhances treatment outcome in post-stroke aphasia. Brain. 2016;139(4):1152–1163. [PubMed: 26912641]

90. Hu X, Zhang T, Rajah GB, et al. Effects of different frequencies of repetitive transcranial magnetic stimulation in stroke patients with non-fluent aphasia: a randomized, sham-controlled study. Neurol Res. 2018;40(6):459–465. [PubMed: 29589518]

91. Wang C-P, Hsieh C-Y, Tsai P-Y, Wang C-T, Lin F-G, Chan R-C. Efficacy of synchronous verbal training during repetitive transcranial magnetic stimulation in patients with chronic aphasia. Stroke. 2014;45(12):3656–3662. [PubMed: 25378426]

Table 1:

Summary of Speech-Language Therapy, tDCS, and rTMS Trials (with >20 participants)

Authors	Design	Participants	Treatment	Dosage	Results
Barbancho et al.[68]	Double-blind, randomized placebo-controlled trial	27 Chronic PSA	CIAT with Memantine Or CIAT with placebo	3 hours/day for 2 weeks Total: 30 hours	Gains on WAB with CIAT; greater gains with memantine + CIAT
Breitenstein et al.[62]	Multicenter, open-label, blinded endpoint randomized controlled trial	156 Chronic PSA	Evidenced-based SLT vs deferral of same SLT for 3 weeks	10 hours a week of individual and group therapy (30+ hours)	Greater gains in language tests with SLT (vs deferral) lasting at least 6 months
De Luca et al.[85]	Randomized, controlled trial	32 Chronic PSA	Power-Afa computer based intervention vs Traditional therapy	45 minute/day 3 days/week for 8 weeks; (18 hours)	Great gains in repetition, selective attention, denomination, and reading with Power-Afa vs traditional
Fleming et al.[29]	Crossover, Randomized controlled trial	35 Chronic PSA	Self-led therapy app Listen-In and standard care blocks	10 hours/week 3 weeks (avg 85 hours)	Greater gains in understanding trained spoken words with Listen-In vs standard, gains maintained at 12 and 24 weeks
Godecke et al.[18]	Phase III, explanatory multicentre, open-label, three arm, blinded end point, parallel group RCT	246 Acute to Subacute PSA	3 arms: Usual Care + 15–20 hours of standard therapy vs. Usual care + 15–20 hours prescribed therapy vs. usual care control	9.5 (SD 7.6) hours over 28 days or 22.7 (SD 8.4) over 32 days	An additional 15–20 hours of therapy (0.34 to 0.71 hours/day) did not improve outcome more than usual care early after stroke
Hilari et al.[86]	Randomized controlled trial, Phase II, explanatory feasibility, single-blind, parallel group	56 Subacute PSA (<6 months)	2 arms: Usual care + peer-befriending vs. usual care control	Six 1-hour peer-befriending visits over three months	Significantly more improvement on a depression scale in the peer-befriending group compared to control group
Palmer et al.[28]	Phase III, pragmatic superiority, multicenter, three arm, single-blind, parallel group RCT	278 Chronic (>4 months) PSA in community	3 arms: Usual care + self- managed computerized speech and language therapy (CSLT) vs. usual care + attention control (puzzle books and phone calls) vs. usual care control	6 months	CSLT plus usual care resulted in a clinically significant improvement in personally relevant word finding but did not result in an improvement in conversation
Woodhead et al.[87]	Baseline-controlled, repeated measures, crossover design	21 Chronic PSA	EG1: iReadMore with anodal TDCS EG2: iReadMore with Sham	Two 4 week blocks; 34 hours of training; 11 stimulation sessions	Improved reading of trained words with iReadMore, small facilitation with anodal stimulation
Noninvasive Brain Stimulation					
Fridriksson et al.[78,88]	Double-blind, randomized sham-controlled trial	74 Chronic PSA	A-TDCS over Area of greatest left hemisphere activation	15 treatment sessions	Significantly greater gains in naming untrained words with A-TDCS vs. sham; especially in participants with val/val BDNF polymorphism
Meinzer et al.[89]	Double blind, randomized, sham-controlled trial	26 Chronic PSA	A-TDCS over Left primary motor cortex	8 days (2×1.5 hours/day)	Improved trained items and Communicative Effectiveness Index scores A-TDCS>sham, lasting 6 months
Sebastian et al.[79]	Randomized double-blind, sham-controlled, cross over	24 Chronic PSA	A-TDCS, C-TDCS, or sham over right cerebellum plus computerized aphasia therapy	30 treatment sessions (15 with A-TDCS or C-TDCS, 15 with sham)	Greater gains in naming (relative to sham) with C-TDCS over right cerebellum for both trained and untrained items
Hu et al.[90]	Double-blind, randomized, sham condition trial	40 Subacute-chronic nonfluent PSA	rTMS: 10 Hz HF vs 1 Hz LF vs sham over Right Broca's area homolog	10 treatment sessions	Greater gains in spontaneous speech, auditory comprehension, and WAB aphasia quotient for LF TMS vs HF TMS or sham

Authors	Design	Participants	Treatment	Dosage	Results
Khedr et al.[82]	Randomized, crossover trial	30 Subacute nonfluent PSA	Right (1Hz) and left (20 Hz) rTMS or sham over Broca's area homolog	10 treatment sessions	Greater gains in word comprehension, naming, repetition, frequency, and aphasia severity in rTMS vs. sham
Rubi-Fessen et al.[81]	Crossover trial	30 Subacute PSA	rTMS 1 Hz or sham over right IFG	10 treatment sessions	Greater gains in functional communication with rTMS vs sham
Tsai et al.[83]	Randomized, sham-controlled trial	56 Chronic nonfluent PSA	rTMS, 1 Hz or sham over right pars triangularis	10 treatment sessions	Greater gains in Concise Chinese Aphasia Test, object naming, and naming reaction time with rTMS vs sham
Wang et al.[91]	Double-blind, randomized trial	45 Nonfluent PSA	rTMS 1 Hz or sham over right Broca's area homolog	10 treatment sessions	Greater gains in action and object naming in rTMS with synchronous SLT vs rTMS with subsequent SLT or sham

Abbreviations: PSA, post stroke aphasia; CIAT, Constraint Induced Aphasia Therapy; SLT, speech-language therapy; WAB, Western Aphasia Battery; SLT, speech-language therapy; A-TDCS, anodal transcranial direct current stimulation; LF, low frequency; HF, high frequency; C-TDCS, cathodal transcranial direct current stimulation; rTMS, Repetitive Transcranial Magnetic Stimulation; Hz, Hertz; BDNF, brain-derived neurotrophic factor; STG, superior temporal gyrus; IFG, inferior frontal gyrus