A Review of Biological Interventions in Chronic Aphasia

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Abstract

Aphasia is a common and debilitating condition following stroke. While the gold standard for aphasia treatment is behavioral speech-language therapy, benefits remain modest in chronic stages of recovery. This limitation motivates the pursuit of novel interventions for chronic aphasia. Here, we review biological approaches that have been used (or proposed for use, in the case of regenerative and genetic therapies) to treat chronic aphasia. These techniques aim to ameliorate the deficits of aphasia by directly manipulating brain function, rather than training lost or compensatory functions, although many have been used to augment effects of behavioral therapy. Specifically, we explore the most robust designs of transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and pharmacotherapy that have been applied in chronic (≥6 months) post-stroke aphasia. We also consider less investigated approaches including epidural cortical stimulation and photobiomodulation. All methods are currently in nascent phases and restricted to experimental studies and clinical trials. Although the evidence base remains limited, such interventions may ultimately improve language function and quality of life for those living with chronic aphasia. However, it is crucial that application of these methods consider the effects of concomitant speech-language therapy, as biological interventions combined with behaviorally induced experience-dependent plasticity will likely yield the most beneficial and durable outcomes.

Keywords: Aphasia, brain stimulation, drug therapy, rehabilitation, stroke

> **Guest editor's notes:** SLT is the bullwork for rehabilitation of PWA. But it has limitations. We cannot continue to rely exclusively on the modest benefits offered by SLT. Can biological interventions help? This review of biological approaches to chronic aphasia likely raises more questions than it answers. We must envision aphasia treatment based on a medical model also, which focuses on repair rather than compensation. The evidence so far is weak or non-conclusive. May be a combination of both approaches will yield better results?

Introduction

Aphasia is a neurological disorder resulting from damage to regions and networks in the human brain that critically support language. This fact – while well known to those who treat it – has not prevented aphasia from being treated primarily using behavioral and educational approaches.[1] The only definitively effective treatment is speech-language therapy (SLT), yet benefits remain modest,[2] falling far short of a cure. Further benefit may be derived from biologically motivated interventions facilitated by greater understanding of normal and disordered neurophysiology. The purpose of this article is to review treatments of chronic aphasia that propose to ameliorate symptoms by directly impacting brain function.

We focus on chronic stages (≥6 months post-onset), as benefits may be more confidently attributed to intervention rather than spontaneous recovery. Additionally, while studies using healthy control subjects and animal models contribute to our understanding of brain processes and recovery, we exclusively examine studies treating participants with aphasia. Finally, although several of the approaches described here have been applied in primary progressive aphasia, we focus here on aphasia produced by focal ischemic injury, the more common type of aphasia, which follows a rehabilitative trajectory distinct from neurodegenerative presentations. All methods are restricted to experimental studies and clinical trials at this time.

Brain Stimulation

Brain stimulation approaches may be divided on the basis of invasiveness, or whether an operative procedure is performed or instrument inserted into the body. While the level of evidence for the best-established interventions remains low to moderate, a recent meta-analysis suggests that effects are stable for up to six months,[3] of crucial importance in aphasia, for which

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maintenance of language improvements over time represents a challenge. This also suggests that these interventions facilitate strengthening or reorganization of language networks.

Many brain stimulation techniques use interhemispheric inhibition (IHI)[4] as the theoretical basis for implementation. On the basis of empirical motor data, IHI proposes that the two cerebral hemispheres have interhemispheric pathways that normally inhibit each other in particular ways and that stroke disrupts them, shifting a balance of function. Uninjured right hemisphere (RH) regions continue to inhibit left hemisphere (LH) language regions. LH regions, disadvantaged by injury, are no longer able to inhibit RH regions as they did previously, allowing RH regions freer rein for overall activity, including increased LH inhibition. Therefore, these approaches typically aim to upregulate the injured LH or downregulate the uninjured RH.

Invasive brain stimulation

Epidural cortical stimulation entails surgical penetration of the skull and placement of an electrode grid/mesh on the dura mater, the outermost meningeal layer. In the only study specifically targeting aphasia, four individuals received implants over the left ventral precentral gyrus with four additional participants as matched controls.[5] All eight non-fluent participants received identical intensive SLT (15 hours/week; six weeks). Stimulators were only active during treatment (amplitude = 4.75-6.5 mA; pulse width = 250 μsec; frequency = 50 Hz) and were removed thereafter. While this was a feasibility and safety study insufficiently powered to detect between-group differences, increases in the Western Aphasia Battery Aphasia Quotient (WAB-AQ) were marginally greater for the stimulation group (very low effect size and very high inter-individual variability), which became more pronounced 12 weeks after treatment as the experimental group continued to improve while the control group regressed. This stimulation advantage was maintained at follow-up intervals ranging from 6 to 21 months.[6] However, placebo effect cannot be ruled out, as participants were aware if they had undergone surgery despite examiner blinding. While epidural cortical stimulation appears safe (based on scant evidence), it is invasive, and the rehabilitative potential of noninvasive stimulation remains to be demonstrated.

Noninvasive brain stimulation
Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) uses an electromagnet to target brain regions with a resolution of approximately one cubic centimeter. Low frequencies (e.g., 1 Hz) are inhibitory while higher frequencies (e.g., 10 Hz) are excitatory. TMS carries a slight possibility of seizure, already a risk in stroke, yet no significant adverse effects have been reported in chronic aphasia. Dose is provided as a percent of resting motor threshold (RMT), determined by inducing hand muscle contraction with single TMS pulses to primary motor cortex. For inclusion in this review, we required studies to have a minimum of five participants and employ both double-blinding and a control condition (e.g., sham TMS). We also excluded studies providing only a single session in each condition,

finding these more experimental than interventional. The five remaining studies [Table 1] had surprisingly similar protocols: all used an inhibitory approach (1Hz) with anatomical targeting of RH inferior frontal gyrus (IFG) using magnetic resonance imaging (MRI) and neuronavigation; 70 mm figure-8 coil; 90% RMT; and five TMS sessions per week. TMS sessions were 10 or 20 minutes, providing 600 or 1200 magnetic pulses, respectively.

Some researchers have used behavioral results to optimize TMS on an individual basis. Comparing six frontal sites, Medina and colleagues used single 10-minute sessions of TMS to inhibit RH ventral primary motor cortex or part of the RH IFG: pars orbitalis (pOrb), pars opercularis (pOp), or a subregion of pars triangularis (pTri).[7] Based on post-stimulation naming, nine of ten participants responded best to pTri suppression; one performed better following pOrb targeting. This process was followed by a crossover study that applied real TMS (or sham) to the individually optimized site for two weeks.[7] At baseline and two months following both phases, participants described the Cookie Theft picture from the Boston Diagnostic Aphasia Examination (BDAE). There was a consistent numerical increase with real vs. sham TMS on multiple discourse measures, yet only use of closed-class words (i.e., determiners, articles, conjunctions, prepositions) reached statistical significance.

In a parallel groups design, 12 individuals received two weeks' TMS targeting RH pTri.[8] The group receiving real stimulation demonstrated significant improvement on the BDAE, including Cookie Theft discourse measures, as well as naming tasks. Notably, on four assessments ranging from one week to one-year post-intervention, improvement of the real TMS group tended to continue, with most significant benefit recorded eight to 12 months later. There were no significant results for the sham group.

The TMS studies above provided stimulation without SLT. Three parallel studies meeting our inclusion criteria paired RH pTri stimulation with language intervention. In the first study, 17 participants performed a picture naming task during real/sham TMS for four weeks, divided into two two-week stages.[9] During the second two-week period, real or sham TMS was followed by three hours of intensive language-action therapy (ILAT; 30 hours total). Both groups benefited significantly on multiple language measures following ILAT, but real TMS conferred no advantage over sham immediately or after three months. Another study provided 56 participants one hour of SLT immediately after ten-minute TMS sessions targeting pTri for two weeks with additional home practice.[10] The real TMS group had scores significantly higher than baseline or sham on the Concise Chinese Aphasia Test (CCAT), which persisted at three-month follow-up; object/action naming accuracy and latency improved immediately following treatment. There was no significant improvement with sham. The final study compared 45 participants who received real or sham TMS with a synchronous picture naming task, or real TMS with the same task 20 minutes later.[11] Participants

Table 1: Summary of double-blind, sham-controlled transcranial magnetic stimulation (TMS) studies (*n* ≥ 5) to treat chronic aphasia

Study	Sample Size/Design	Aphasia Type/ Severity	MPO (SD) [Range]*	Method†/Duration/# Sessions	Concomitant Therapy	Outcome‡
Medina *et al.* (2012)[7]	10 (partial crossover with 5 real; 5 sham-initial followed by real)	Non-fluent (mild to moderate)	50.20 (30.81) [6-102]	1 Hz to individually optimized RH IFG site; 5 × 10 min/wk × 2 wks	None	Real > sham increase for closed class words but not other discourse measures
Barwood *et al.* (2013)[8]	12 (parallel groups with 6 real; 6 sham)	Non-fluent (mild-moderate to severe)	41.52 (18.36) [26-75]	1 Hz to RH pTri; 5 × 20 min/wk × 2 wks	None	Real > sham increase on multiple language measures at 2 to 12 mos but not 1 wk post
Tsai *et al.* (2014)[10]	56 (parallel groups with 33 real; 23 sham)	Non-fluent (mild to severe; Broca's, TCM, global)	18.01 (7.56) [> 3]	1 Hz to RH pTri; 5 × 10 min/wk × 2 wks	5 × 60 min/wk SLT (< 30 min after TMS) + 5 × 30 min home training × 2 wks	Real > sham increase on CCAT, action / object naming accuracy / reaction time immediately post; CCAT increases maintained × 3 mos
Wang *et al.* (2014)[11]	45 (parallel groups with 15 real + synchronous task; 15 real + subsequent task; 15 sham + synchronous task)	Non-fluent (Broca's, TCM, global)	16.20 (7.29) [> 6]	1 Hz to RH pTri; 5 × 20 min/wk × 2 wks	5 × 20 min/wk picture naming (during or immediately after TMS) + 2 × 60 min/wk SLT × 2 wks	Synchronous TMS > subsequent / sham increase on CCAT and action / object naming (maintained × 3 mos for naming). No difference between subsequent vs. sham.
Heikkinen *et al.* (2019)[9]	17 (parallel groups with 9 real; 8 sham)	Fluent and non-fluent	40.59 (26.13) [11-96]	1 Hz to RH pTri; 5 × 20 min/wk × 4 wks	5 × 20 min/wk naming during TMS × 2 wks followed by 5 × 180 min/wk Intensive Language Action Therapy after TMS × 2 wks	No difference between real and sham on Western Aphasia Battery, Boston Naming Test, Action Naming Test

*Minimum provided where range was not available. †All studies used magnetic resonance imaging (MRI) and neuronavigation for targeting. ‡Results reported based on statistical significance. MPO=Months post-onset, SD=Standard deviation, RH=Right hemisphere, IFG=Inferior frontal gyrus, pTri=Pars triangularis of IFG; TCM=Transcortical motor; SLT=Speech-language therapy, CCAT=Concise Chinese Aphasia Test

also received one hour of biweekly SLT during these two weeks. Both real TMS groups improved significantly on the CCAT immediately and at three-month follow-up, while the sham group did not. The synchronous TMS group improved significantly on object/action naming at both post-assessments, and most post-treatment scores were significantly higher on the CCAT and naming tasks for synchronous TMS compared to both other conditions.

Overall, these studies suggest that inhibitory TMS to RH pTri has the potential to durably benefit language in chronic aphasia. While some studies have instead excited the left hemisphere, targeted posterior regions, or selected the hemispheric target using functional MRI (fMRI), none of these had adequate samples, controls, or blinding to permit discussion here. Single sessions of TMS may also provide insight into language organization and recovery potential, despite not qualifying, by our judgment, as therapeutic interventions. Additionally, no studies using theta burst stimulation (TBS), a newer form of TMS that can greatly decrease session duration, met the inclusion criteria. Given the paucity of robust TMS research in chronic aphasia, its noninvasive nature, and the promising results of this research, further study is needed.

Transcranial electrical stimulation

Transcranial electrical stimulation (tES) uses weak electrical currents to modulate neural activity. At least one electrode is applied to the scalp with at least one additional electrode completing the circuit, typically elsewhere on the head. Dosing includes electrode size/placement (montage), current intensity/ duration, and session number/frequency. Unlike TMS, tES modulates function instead of causing action potentials in underlying brain tissue. Thus, it is generally accepted that tES effects depend on concurrent activity,[12] and we restrict our review to studies including behavioral tasks. We further restrict studies to those including at least five participants, double-blinding, and a control condition (sham, alternate montage) with more than one session in each condition.

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is the primary form of tES that has been applied in chronic aphasia. Anodal (positive) electrodes are believed to increase cortical excitability, with cathodal (negative) stimulation believed to inhibit underlying cortex. The most common approach is to provide anodal stimulation to LH language regions. Often the placement of one electrode is motivated by an anatomical hypothesis, with the

Table 2: Summary of double-blind, sham-controlled transcranial direct current stimulation (tDCS) studies (*n* ≥ 5) paired with behavioral tasks to treat chronic aphasia

			Conventional sponge-based transcranial direct current stimulation (tDCS)				
Study	Sample Size/Design	Aphasia Type/ Severity	MPO (SD) [Range]*	Intensity/ Duration/# Sessions†	Method/Target‡	Concomitant Therapy	Outcome§
Baker *et al.* (2010)[13]	10 (crossover with 1-wk washout)	Fluent and non-fluent (anomic, Broca's)	64.60 (68.42) [10-242]	1 mA; 5 × 20 min/wk × 1 wk	Anode (25 cm²): frontal LH guided by task-based fMRI; Return (25 cm²): right shoulder	5 × 20 min/wk computer-based word-picture matching task × 1 wk	Active > sham increase on naming trained/ untrained items immediately and 1 wk post
Flöel *et al.* (2011)[25]	12 (crossover with 3-wk washout)	Fluent and non-fluent (anomic, Wernicke's, Broca's, global)	84.17 (65.35) [14-260]	1 mA; 2 × 20 min/day × 3 days	1) Anode (35 cm²): temporo-parietal RH; Return (100 cm²): right forehead 2) Cathode (35 cm²): temporo-parietal RH; Return (100 cm²): right forehead	2 × 60 min/day computer-based naming training × 3 days	Anode / cathode > sham increase on naming trained items immediately post; anode > sham increase maintained 2 wks post
Fridriksson *et al.* (2011)[18]	8 (crossover with 3-wk washout)	Fluent	58.38 (44.60) [10-150]	1 mA; 5 × 20 min/wk × 1 wk (5 min after task began)	Anode (25 cm²): posterior LH guided by task-based fMRI	5 × 25 min/wk computer-based word-picture matching task × 1 wk	Active > sham decrease on naming latency for trained items (only) immediately and 3 wks post
Vines *et al* (2011)[23]	6 (crossover with 1-wk washout)	Non-fluent (Broca's; moderate to severe)	55.00 (37.71) [30-120]	1.2 mA; 1 × 20 min/day × 3 days	Anode (16.3 cm²): RH IFG (2.5 cm posterior to F8); Return (30 cm²): left forehead	1 × 20 min/ day Melodic Intonation Therapy × 3 days	Active > sham decreased utterance duration on verbal fluency battery
Fiori *et al.* (2013)[22]	7 (crossover with 6-day washout)	Non-fluent	32.86 (27.94) [7-84]	1 mA; 5 × 20 min/wk × 3 wks	1) Anode (35 cm²): LH IFG (F5) 2) Anode (35 cm²): temporo-parietal LH (CP5)	5 × 20 min computer-based noun or verb naming × 3 wks (one month interval between)	F5 > CP5 / sham increase in verb naming; CP5 > F5 / sham increase in noun naming; effects maintained for 4 wks
Marangolo *et al.* (2013)[21]	12 (crossover with 2-wk washout)	Non-fluent	37.25 (22.16) [7-84]	1 mA; 5 × 20 min/wk × 2 wks	1) Anode (35 cm²): LH IFG (F5) 2) Anode (35 cm²): temporo-parietal LH (CP5)	5 × 120 min/ wk multimodal conversational SLT × 2 wks	F5>CP5 / sham increase on production of content units, verbs, sentences for describing trained videos (maintained for 4 wks) and some measures for untrained videos
Marangolo *et al.* (2013)[26]	8 (crossover with 2-wk washout)	Non-fluent + severe apraxia of speech	29.00 (25.21) [6-74]	2 mA; 5 × 20 min/wk × 2 weeks	Anode (35 cm²): LH IFG (F5); Cathode (35 cm²): RH IFG (F6)	5 × 60 min/wk imitation-based SLT × 2 wks	Active > sham increase in accuracy / reaction time for word / sentence repetition immediately and after 4 wks
Volpato *et al.* (2013)[17]	8 (crossover with no washout reported)	Fluent and non-fluent (mild to moderate; anomic, TCS, conduction, Wernicke's, Broca's, TCM)	27.00 (41.21) [6-126]	2 mA; 5 × 20 min/wk × 2 wks	Anode (35 cm²): LH IFG (FC5)	"Standard" SLT unrelated to experiment provided ≥ 90 min before/after tDCS	No difference between active and sham on accuracy / response time for object / verb naming

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Conventional sponge-based transcranial direct current stimulation (tDCS)

Marangolo *et al.* (2014)[28]	7 (crossover with 2-wk washout)	Non-fluent (severe)	32.29 (25.31) [6-74]	2 mA; 5 × 20 min/wk × 2 wks	Anode (35 cm²): LH IFG (F5); Cathode (35 cm²): RH IFG (F6)	5 × 90 min/wk pragmatic SLT × 2 wks	Active > sham increase on picture description, noun / verb naming immediately and 1 wk post
Campana *et al.* (2015)[15]	20 (crossover with 2-wk washout)	Non-fluent	35.2 (23.62) [6-84]	2mA; 5 × 20 min/wk × 2 wks	Anode (35 cm²): LH IFG (F5)	5 × 60 min/wk conversational SLT × 2 wks	Active > sham increase in noun / verb naming, picture description immediately post
Cipollari *et al.* (2015)[24]	6 (crossover with 2-wk washout)	Non-fluent + severe apraxia of speech	38.83 (30.85) [10-79]	2 mA; 5 × 20 min/wk × 3 wks	Anode (35 cm²): RH IFG (F8)	5 × 20 min/ wk Melodic Intonation Therapy × 3 wks	Active > sham increase on correct word / sentence repetition immediately post, maintained × 1 wk
de Aguiar *et al.* (2015)[29]	9 (crossover with 2-wk washout)	Fluent and non-fluent	48.89 (31.34) [8-92]	1 mA; 5 × 20 min/wk × 2 wks	Anode (35 cm²): frontal (*n*=8) or posterior (*n*=1) LH region guided by anatomical MRI; Return (35 cm²): RH homologue or IFG (FC6)	5 × 60 min/wk verb naming/ production SLT × 2 wks	Active > sham increase on trained / untrained verb production
Marangolo *et al.* (2016)[27]	9 (crossover with 2-wk washout)	Non-fluent + severe apraxia of speech	39.56 (32.29) [7-96]	2 mA; 5 × 20 min/wk × 3 wks	Anode (35 cm²): LH IFG (F5); Cathode (35 cm²): RH IFG (F6)	5 × 60 min/wk imitation-based SLT × 3 wks	Active > sham increase on accuracy for syllable / word repetition immediately post
Meinzer *et al.* (2016)[16]	26 (parallel groups with 13 active; 13 sham)	Fluent and non-fluent (anomic, Wernicke's, Broca's, global)	45.73 (24.84) [15-108]	1 mA; 2 × 20 min/day × 3 days	Anode (35 cm²): LH primary motor cortex (C3); Return (100 cm²): right forehead	2 × 90 min/day computer-based naming training × 4 days × 2 wks	Active > sham increase on naming untrained items, CETI immediately post and naming trained / untrained items, PCQ at 6 mos
Fridriksson *et al.* (2018)[19,20]	74 (parallel groups with 34 active; 40 sham)	Fluent and non-fluent (anomic, conduction, Wernicke's, Broca's, TCM, global)	41.84 (39.67) [> 6]	1mA; 5 × 20 min/wk × 3 wks	Anode (25 cm²): posterior LH guided by task-based fMRI	5 × 45 min/wk computer-based word-picture matching task × 3 wks	Active > sham increase on naming trained / untrained items immediately and at 4 and 24 wks post
Marangolo *et al.* (2018)[30]	12 (crossover with 6-day washout)	Non-fluent (mild)	21.58 (6.93) [14-37]	2mA; 5 × 20 min/wk × 1 wk	Cathode (35 cm²): right cerebellum (1 cm under and 4 cm lateral to inion);Return (35 cm²): right shoulder	1) 5 × 20 min/wk computer-based verb naming × 1 wk 2) 5 × 20 min/wk computer-based verb generation × 1 wk	Active > sham increase on accuracy / reaction time for verb generation immediately and 1 wk post; no difference for verb naming
Woodhead *et al.* (2018)[14]	21 (crossover with 4-wk washout)	Aphasia + central alexia	59 (39)[12-158]	2mA; 3 × 20 min/wk × 4 wks	Anode (35 cm²): LH IFG (FC5)	3 × 40 min/wk computer-based reading training + home practice × 4 wks (35 hrs total)	Active > sham increase on reading trained / untrained words immediately post; sham > active increase in written semantic matching

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High-definition transcranial direct current stimulation (HD-tDCS)

Richardson *et al.* (2015)[31]	8 (crossover with 1-wk washout)	Fluent and non-fluent (anomic, Broca's)	100.25 (91.98) [9-312]	1mA (conventional tDCS), 2mA (HD-tDCS); both 5 × 20 min/wk × 1 wk	1) Conventional tDCS=Anode (25 cm²): posterior LH guided by task-based fMRI 2) HD-tDCS=2 anodes and 2 cathodes with individualized placement to target same posterior LH region	5 × 20 min/wk computer-based word-picture matching task × 1 wk	No difference between conventional and HD-tDCS on naming trained / untrained items immediately or 1 wk post (no sham condition)
Fiori *et al.* (2019)[32]	20 (crossover with 1-wk washout)	Non-fluent	40 (18.52)[>6]	1mA (Group 1) or 2mA (Group 2); 5 × 20 min/wk × 1 wk	Cathode (12 mm diameter ring electrode): RH IFG (F6); Return: 4 equal sized/ spaced electrodes 3.5 cm from cathode	5 × 20 min/wk computer-based verb naming task × 1 wk	2mA > 1mA / sham increase on verb naming immediately and 1 wk post; no difference between 1mA and sham

*Minimum provided where range was not available.†Unless otherwise specified, stimulation and therapy/task began concurrently. ‡Electrode of opposite polarity is cited as "return" unless intended to have physiological effect. Unless otherwise stated, "return" electrode was same size as target electrode and placed on contralateral forehead. §Results reported based on statistical significance. MPO=Months post onset, SD=Standard deviation, LH/RH=Left/right hemisphere, (f)MRI=(functional) Magnetic resonance imaging, IFG=Inferior frontal gyrus, TCS/TCM=Transcortical sensory/motor, CETI=Communicative Effectiveness Index, PCQ=Partner Communication Questionnaire
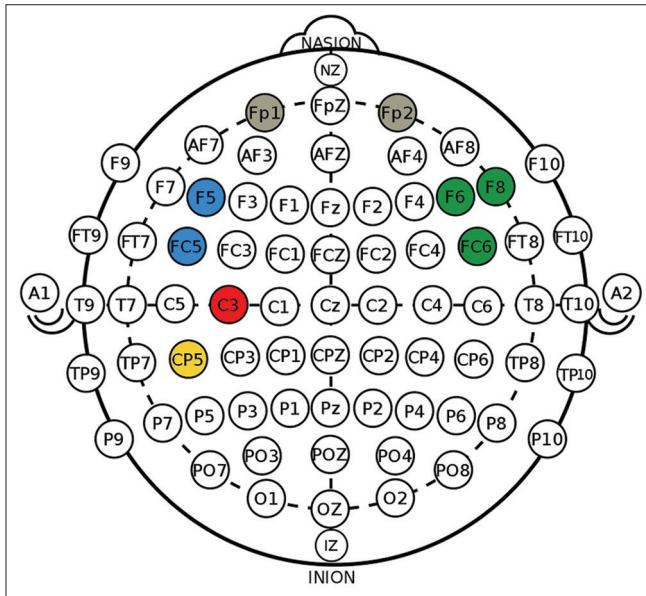

Figure 1: EEG 10-10 electrode placements used in transcranial direct current stimulation (tDCS) to treat chronic aphasia [from Table 2; additional sites have been used in other studies]. Left = odd numbers, right = even numbers. Sites used to target Broca's area in blue, right Broca's homologue in green, primary motor cortex in red, and Wernicke's area in yellow. Sites frequently used as "return" (i.e., to close the circuit without any specific anatomical motivation) are in gray (typically placed contralateral to target electrode)

other electrode(s) viewed simply as "return," potential effects of which are summarily ignored. Most studies below use the contralateral forehead as "return," 1 mA intensity, 20-minute duration, and five sessions per week [see Table 2 for details], and nearly all are crossover studies (durations indicated are per

condition). With relatively diffuse stimulation (electrodes usually measure 25–35 cm²), tDCS studies often rely on the EEG 10-10 head measurement system for electrode placement [Figure 1]; odd (even) numbers are assigned to the LH (RH). Frequently used sites include F5, F7, and FC5 to target Broca's area and CP5 to target Wernicke's area.

Left frontal excitation

Most tDCS research in chronic aphasia applies anodal stimulation to LH frontal regions. In the earliest treatment study, ten patients received active or sham stimulation paired with one week of computerized word-picture matching treatment.[13] The anode was placed on a left frontal site localized by identifying individual fMRI activation on a naming task. Naming accuracy for treated and untreated items was significantly improved for the active stimulation phase compared to sham immediately and at one-week follow-up. Another crossover study using a computer-based reading program (12 sessions over four weeks with home practice) found 21 participants receiving anodal stimulation over Broca's area benefited significantly on reading of trained and untrained words, with effects for trained words maintained for three months.[14] Benefit has also been documented for tasks not directly tied to therapy. Twenty participants who received anodal tDCS over Broca's area at the beginning of one hour of conversational SLT improved significantly on noun/verb naming and picture description immediately following the two-week active tDCS phase compared to sham.[15] Further, a parallel design used anodal stimulation over primary motor cortex in 26 participants receiving treatment twice daily for eight days across two weeks during computerized naming therapy.[16] Performance on untrained items was significantly better immediately

post-treatment for active tDCS vs. sham, and for both trained and untrained items at six-month follow-up.

The effective tDCS studies applied synchronous behavioral therapy. Eight participants who received ten sessions of SLT ≥90 minutes before or after tDCS found no significant difference between active and sham phases.[17] This is consistent with subthreshold effects of tDCS, believed to potentiate co-occurring neural activity.

Left posterior excitation
An early crossover study of participants with fluent aphasia targeted the posterior LH based on maximal fMRI activation during naming.[18] Following one week of tDCS with simultaneous computer-based word-picture matching treatment, a significant reduction in response time was found for trained (but not untrained) words immediately post-treatment and at three-week follow-up. Subsequently, a large ($n = 74$) parallel design used the same targeting method and therapy for three weeks, finding significant improvement in the active tDCS group compared to sham immediately and at four- and 24-week post-assessments.[19] Follow-up analysis indicated superiority of active vs. sham tDCS for trained and untrained items.[20] These studies suggest that posterior LH regions are also legitimate stimulation targets.

Left frontal vs. posterior excitation
Two studies have contrasted effects of anodal left frontal, posterior, and sham tDCS. Following two weeks of tDCS paired with two-hour sessions of conversational SLT, participants produced more content units, verbs, and sentences immediately after frontal tDCS compared to posterior or sham stimulation, with effects maintained for four weeks.[21] Another study used the same stimulation protocol (and apparently mostly the same participants) with an object/action naming task for one week.[22] Significantly more nouns were produced one week after posterior tDCS, while significantly more verbs were produced following frontal tDCS. Four weeks post-treatment these findings were both significantly greater than sham and the other active condition, suggesting that different targets can enhance different skills in the same individuals.

Right frontal excitation
Two crossover studies have used Melodic Intonation Therapy (MIT) with anodal stimulation of RH frontal regions. In six participants, anodal tDCS was applied over RH IFG. Following stimulation paired with MIT for three consecutive days, active tDCS resulted in a significant reduction in time required to produce the same utterances compared to sham.[23] A second study applied anodal tDCS over RH IFG during MIT, also in six participants, across three weeks.[24] Significant improvement was recorded for repeating trained words/sentences in both conditions immediately after treatment and at one-week follow-up, with immediate results significantly higher for active tDCS. As few studies have applied excitatory tDCS to RH regions, it remains an open question whether similar results might be observed with therapies not theorized to principally affect the RH (as is MIT).

Right posterior excitation vs. inhibition
One crossover study of 12 participants selected a site based on fMRI activation associated with greater long-term success in naming trained objects (different participants; no tDCS).[25] Stimulation was applied twice daily during two hours of computer-based naming therapy to this RH temporoparietal site for three consecutive days. Anodal tDCS resulted in significant improvement over sham immediately after training and at two-week follow-up, while cathodal tDCS was less effective (immediate improvement only). Theoretical models notwithstanding, the impact of tDCS, and the role of the RH in aphasia recovery remains to be established.

Bi-hemispheric stimulation
A few crossover studies have used a symmetrical bi-hemispheric approach by applying anodal tDCS to left IFG and cathodal tDCS to the RH homologue. Eight participants with non-fluent aphasia and apraxia of speech (AOS) participated in imitation-based SLT for two weeks.[26] With active tDCS but not sham, they improved significantly in accuracy and reaction time on measures of repetition (syllables, words, and sentences) immediately following treatment and one week later. Using the same SLT for three weeks, nine participants improved significantly on syllable and word repetition immediately after treatment with active tDCS compared to sham.[27] A third study provided seven participants with pragmatic conversational SLT for two weeks, evaluating effects on picture description and object/verb naming.[28] All tasks showed significant benefit with active tDCS vs. sham, which were maintained one week later. The final bi-hemispheric study determined stimulation site individually (based on anatomical MRI), with anodal frontal placement for eight of nine participants and cathode typically over the homologue.[29] Following two weeks of verb-oriented sentence production therapy, verb production in active and sham improved to equal levels, although scores had been significantly lower before the active phase. These results support benefits of bi-hemispheric tDCS, highlighting the need for direct comparison with the more frequently used montages described above.

Cerebellar stimulation
One crossover study capitalized on the existence of contralateral connections with the LH by disinhibiting the right cerebellum (i.e., suppressing GABAergic Purkinje cells).[30] In 12 participants, cathodal stimulation was administered during verb naming (given action pictures) and generation (given associated object images) over one week. Significant improvement for active tDCS vs. sham was only recorded for the more complex verb generation task.

High-definition tDCS
In high-definition tDCS [HD-tDCS; Table 2], smaller electrodes (~1 cm diameter) are used to provide more flexible and focal stimulation. Contrasting conventional and HD-tDCS, eight individuals participated in two five-day phases of computerized word-picture matching therapy during stimulation over a left temporal region defined individually

using fMRI.[31] For conventional tDCS, the anode was placed on the scalp over this region; for HD-tDCS, the location of two anodes and two cathodes was determined individually based on current modeling for maximal intensity at the targeted region. Naming accuracy for trained items improved significantly (maintained for one week) yet no statistical difference was demonstrated between conditions. Another study applied cathodal stimulation to RH Broca's homologue, encircled by four anodal electrodes.[32] Two groups of ten individuals received either 1 or 2 mA tDCS (also sham) during five sessions of a verb retrieval task. Individuals performed significantly better on verb naming with 2 mA compared to 1 mA or sham immediately and at one-week follow-up, with no significant difference between 1 mA and sham. The typically closer placement of electrodes in HD-tDCS means that less current may penetrate the skull, potentially resulting in lower effects of current intensities equivalent to those used in conventional tDCS.

Other forms of transcranial electrical stimulation

While tDCS uses a constant current, other underexplored forms of tES rely on different waveforms to modulate brain function. Transcranial alternating current stimulation (tACS) applies a sinusoidal current that fluctuates between positive and negative and may help coordinate neural oscillations between regions. Transcranial pulsed current stimulation (tPCS) alternates current polarity using a rectangular waveform. Transcranial random noise stimulation (tRNS) may be useful to disrupt activity of "noisy nodes." While no known study has employed tPCS or tRNS in aphasia, one study ($n = 98$) administered tACS in a stroke recovery study, reporting improved word selection and speech rate for the subpopulation with aphasia ($n = 21$).[33]

Transcranial electrical stimulation summary

As tES systems are relatively safe, portable, and inexpensive, they offer great promise for translation into the clinic. However, most included studies employed computer-based treatments, rather than individualized therapy provided by a skilled professional and current findings are underpowered and heterogeneous. Studies suggest benefit (with generally modest effects) for various tDCS protocols, with limited comparisons between these. Other forms of tES are essentially unexplored.

PHARMACOTHERAPY

Drug treatment is standard for many neurological disorders, but there is currently no accepted or approved pharmacological intervention for aphasia. Pharmacotherapy in chronic aphasia is challenging due to the complex nature of language and the dependence of neuroplasticity on various neurotransmitters (e.g., acetylcholine, dopamine, norepinephrine, serotonin), all of which are interrupted by stroke.[34] The brain's primary excitatory and inhibitory neurotransmitters, glutamate and GABA respectively, are also crucial for normal language processing.[34] This wide variety of legitimate biological targets for potentially improving post-stroke aphasia offers many options for pharmacological intervention. We review those

that have been used in chronic aphasia, restricting inclusion to double-blind studies reporting use of placebo [$n \geq 5$; Table 3].

Dopamine modulation

The neurotransmitter dopamine plays a critical role in motivation, reward, and executive functioning. Bromocriptine, a dopamine agonist, is used to treat Parkinson's disease and has been used in multiple trials of chronic aphasia. While receiving up to 30 mg of bromocriptine daily with an unspecified amount of biweekly SLT, five participants demonstrated improved performance on several language measures.[35] However, performance on most measures diminished following cessation of SLT despite continuation of bromocriptine. Placebo and SLT began simultaneously and always preceded the active drug phase, making it impossible to disentangle their individual contributions; significant results reported for bromocriptine were comparisons with baseline rather than placebo. Of additional concern, side effects attributable to bromocriptine (cardiac arrhythmia, visual hallucinations, nausea, syncope) were present in five of seven participants, resulting in removal of two participants prior to study completion. Two additional studies found no effect in patients treated with doses of 15 mg daily ($n = 20$)[36] or up to 60 mg daily ($n = 7$).[37] Importantly, these two trials included no behavioral intervention. Additional studies suggest that bromocriptine may require titration on an individual basis, and that aphasia severity may also play a role.

Levodopa is commonly used to increase dopamine levels in Parkinson's disease and has been reported in one study of chronic aphasia.[38] This crossover study combined levodopa with carbidopa, which inhibits levodopa's peripheral metabolism, permitting more of it to reach the brain. The study was halted after ten participants (of 20 planned) due to conclusive results that levodopa administered prior to SLT provided no benefit compared to placebo. High-intensity SLT (40 hours in two weeks) may have obscured improvement that might have been observed with a more standard therapy schedule (or without treatment).

Acetylcholine modulation

Acetylcholine is produced by nuclei deep within the brain that project widely to cortical regions and critically influence arousal, attention, learning, and memory. Donepezil, a cholinesterase inhibitor, increases acetylcholine availability in the brain by acting on enzymes that normally break it down. A single crossover study pairing a computerized phonological training with donepezil (≤ 10 mg $\times$ 10 weeks) unexpectedly found significantly poorer auditory comprehension with donepezil compared to placebo in 20 participants.[39] In a parallel group study, 26 participants received biweekly behavioral therapy (2.5 total hours/week) coupled with 12 weeks of daily donepezil (≤ 10 mg). The drug group demonstrated significant improvement on the WAB-AQ and the object naming subtest of the Psycholinguistic Assessments of Language Processing Abilities (PALPA) compared to placebo.[40] Immediate effect sizes were large, yet between-group differences were not

Table 3: Summary of pharmacological studies in chronic aphasia (*n* ≥ 5) reporting double-blind conditions and use of placebo

Study	Sample Size/ Design	Aphasia Type/Severity	MPO (SD) [Range]*	Drug/Dose/ Duration	Control	Therapy Type/Dose	Outcome†
Gupta *et al.* (1995)[36]	20 (crossover with 4-wk washout)	Non-fluent (Broca's, TCM, "mixed anterior")	66.75 (63.28) [13-207]	Bromocriptine (increased to 15 mg/day by wk 3) × 8 wks; then 2-wk dose reduction	Placebo × 8 wks; then 2-wk "dose" reduction (order counterbalanced)	None	No difference between drug and placebo on speech fluency, language content, aphasia severity
Sabe *et al.* (1995)[37]	7 (crossover with 3-wk washout; placebo as second arm)	Non-fluent (mild to severe; Broca's, TCM, global)	30 (no data) [12-84]	Bromocriptine (increased to 60 mg/day by wk 5) × 6 wks	Placebo × 6 wks in second arm only	None	No difference between drug and placebo on naming, verbal fluency, picture description
Huber *et al.* (1997)[43]	66 (parallel groups with 32 drug; 34 placebo)	Fluent and non-fluent (anomic, Wernicke's, Broca's, global)	10.56 (11.33) [1-36]	Piracetam (4.8 g/day) × 6 wks	Placebo × 6 wks	5 × 60 min/wk individual SLT + 5 × 60 min/wk group SLT × 6 wks	Drug > placebo increase on written language subtest of AAT; no significant difference for other measures
Bragoni *et al.* (2000)[35]	11 total; 5 completed (crossover with placebo as first arm)	Non-fluent (mild to severe; Broca's, global)	2.14 (2.21) [6-96]	Bromocriptine (increased to 30 mg/day by wk 4) + antiemetic (domperidone) × 18 wks	Placebo × 9 wks + antiemetic (domperidone) in first arm only	Individual SLT 2×/wk (unspecified duration) × 18 weeks (9 wks + placebo and 9 wks + drug)	Drug vs. placebo not reported; increase on 4 of 14 language measures with drug + SLT vs. baseline
Berthier *et al.* (2006)[40]	26 (parallel groups with 13 drug; 13 placebo)	Fluent and non-fluent (mild to severe; anomic, conduction, Wernicke's, Broca's)	36.0 (30.5) [> 12]	Donepezil (increased to 10 mg/day by week 5) × 16 wks	Placebo × 16 wks	120 min/wk "standard" SLT (unspecified frequency) × 16 wks	Drug > placebo increase on WAB-AQ and picture naming subtest of PALPA; placebo > drug maintenance 4 wks post-treatment on CAL
Tsikunov & Belokoskova (2007)[42]	26 (crossover with placebo as first arm)	Fluent (mild to severe; classified as acoustico-amnestic or acoustico-agnostic)	16.8 (1.2) [12-24]	Desmopressin (intranasal; 0.1 µg single dose) × 6-8 wks (4 µg total dose)	Placebo × 2 wks (intranasal saline) in first arm only	None	Drug > placebo increase for both aphasia types on "independent speech", automatic speech, naming
Berthier *et al.* (2009)[41]	28 total; 27 completed (parallel groups with 14 real; 13 placebo)	Fluent and non-fluent (mild to severe; anomic, conduction Wernicke's, Broca's, TCM)	49.85 (73.72) [12-384]	Memantine (increased to 20 mg/day by wk 3) × 20 wks followed by 4-wk washout	Placebo × 20 wks followed by 4-wk washout	5 × 180 min/wk constraint-induced aphasia therapy (CIAT; 2-3 participants per group) × 2 wks (wks 18-20)	Drug > placebo increase on WAB-AQ with/without CIAT and following washout; drug > placebo improvement on CAL immediately post-CIAT
Breitenstein *et al.* (2015)[38]	10 (crossover with 4-wk washout)	Fluent and non-fluent (moderate to severe; Wernicke's, Broca's, global)	6.3 (3.4) [> 12]	Levodopa (100 mg) + carbidopa (25 mg) × 5 days × 2 wks (each dose provided 90 min prior to therapy)	Placebo × 5 days × 2 wks (90 min prior to therapy) (order counterbalanced)	5 × 180 min/wk naming exercises + 5 × 60 min/wk conversational training × 2 wks	No difference between drug and placebo on naming trained / untrained items or ANELT (conversational scenarios), CAL, SAQOL-39

Contd...

Study	Sample Size/ Design	Aphasia Type/Severity	MPO (SD) [Range]*	Drug/Dose/ Duration	Control	Therapy Type/Dose	Outcome[†]
Woodhead *et al.* (2017)[39]	20 (crossover with 5-wk washout)	Fluent and non-fluent (moderate to severe; Wernicke's, global)	40.23 (30.98) [7-103]	Donepezil (increased to 10 mg/day by wk 6 when therapy was introduced) × 10 wks	Placebo × 10 wks (order counterbalanced)	2 × 40 min/day computer-based phonological training (Earobics) + drug/ placebo × 5 wks (wks 6-10 of each arm). All at home (~75% compliance).	Placebo > drug increase on one CAT subtest (speech comprehension); no difference for other CAT subtests, SART, ASHA FACS

*Minimum provided where range was not available. [†]Results reported based on statistical significance. MPO=Months post onset, SD=Standard deviation, TCM=Transcortical motor, SLT=Speech-language therapy, AAT=Aachen Aphasia Test, WAB-AQ=Western Aphasia Battery Aphasia Quotient, PALPA=Psycholinguistic Assessments of Language Processing Abilities, CAL=Communicative Activity Log, ANELT=Amsterdam-Nijmegen Everyday Language Test, SAQOL-39=Stroke and Aphasia Quality of Life Scale-39, CAT=Comprehensive Aphasia Test, SART=Sustained Attention to Response Task, ASHA FACS=American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults

maintained following four-week washout. If beneficial, donepezil does not appear to induce lasting neuroplasticity.

Memantine

Memantine is a noncompetitive antagonist at glutamatergic NMDA receptors that is currently used to treat cognitive symptoms of Alzheimer's disease. A single randomized controlled trial of 27 patients evaluated effects of memantine with drug (or placebo) provided in isolation both before and after periods of constraint-induced aphasia therapy (CIAT).[41] Memantine was provided for 20 weeks with CIAT provided during weeks 16–18 and a washout period from weeks 20–24. Significant improvement occurred on the WAB-AQ for memantine compared to placebo, with large effect sizes before, during, and after therapy. A medium effect still favored the memantine group following the four-week washout, despite both groups benefiting from CIAT.

Vasopressin

Vasopressin is an antidiuretic hormone produced by the hypothalamus that is believed to play a role in mediating social behavior and cognitive function. In the single extant study of vasopressin in aphasia, 26 patients received two weeks of placebo followed by 1.5 to two months of intranasal desmopressin (synthetic vasopressin).[42] Statistically significant results with long-term maintenance were reported across a number of language measures, although the weak design (nonequivalent placebo condition always first) tempers confidence in these results.

Piracetam

Piracetam is a derivative of the inhibitory neurotransmitter GABA that has been said to benefit cognitive function despite poorly understood mechanisms. One study provided 24 patients with piracetam and 26 with placebo.[43] Most, but not all, were in chronic stages of stroke recovery. All participated in high intensity SLT (10 hours/week × 6 weeks). Although the piracetam group showed some numerical improvement on the overall profile of the Aachen Aphasia Test (AAT) and component subtests, this was not significant.

One subtest, written language, showed statistically significant between-group effects, but was not a primary endpoint.

Pharmacology summary

Effects of bromocriptine are questionable with concerning side effects. Levodopa has no current foundation for support, and piracetam effect also remains to be established. Donepezil appears unlikely to provide benefit beyond the treatment period, whereas memantine and vasopressin may offer promise if results can be replicated. While we included only studies reporting double-blinding and use of placebo, some of the designs were particularly weak (i.e., placebo consistently first/second in crossover studies or administered for different duration than drug). As all findings are based on one to three studies, caution is recommended in interpreting results.

This overview excluded several studies (and drugs) showing significant effects, either due to open-label administration, lack of blinding, or small sample size. However, most reviews of pharmacotherapy in aphasia have combined acute/subacute patients with chronic ones; these groups are certain to differ in recovery mechanisms and response to intervention. Overall, evidence for pharmacological improvement of chronic aphasia is weak. Future studies need to employ more robust designs. In addition to equivalent placebo controls, studies should contrast effects with and without concomitant behavioral therapy to determine whether some drugs might be productive as adjuvant treatments and others indicated when SLT is not available.

Photobiomodulation

Photobiomodulation, also known as low-level light therapy, makes use of the long, penetrating waveforms of red and near-infrared light to irradiate underlying tissue. Initially employing lasers, current applications predominantly rely on safe light-emitting diodes (LEDs) and are often used on peripheral skeletal tissue. Proposed mechanisms of effect include increased local vasodilation with consequent increased blood flow, and increased production of adenosine triphosphate (ATP), a crucial provider of energy for many cellular processes. Photobiomodulation has

also been suggested to increase antioxidant mechanisms and upregulate neuroprotective genes. More recently, transcranial photobiomodulation (tPBM) has been applied to the head to influence metabolic properties of brain tissue. In the sole study using tPBM to treat aphasia, various subsets of six participants underwent four montages.[44] The most effective montage targeted the ipsilesional hemisphere and midline structures of the default mode network, while the least effective montage included contralesional targets. We anticipate future studies using tPBM will illuminate potential effectiveness in chronic aphasia.

REGENERATIVE/GENETIC THERAPIES

While the approaches discussed above target language function by optimizing synapses connecting surviving neurons, regenerative therapies aim to regrow lost tissue (and subsequently integrate neurons into existing dysfunctional networks to adaptively ameliorate behavioral deficits). Despite considerable speculation on stem cell therapies and tissue transplantation in human stroke recovery, these remain poorly investigated. To date, most studies focus on acute stroke, and all report on safety and feasibility and/or address only motor outcomes. Although no stem cell studies have provided measures of language, significant improvement has been reported in chronic stroke for some cognitive and affective measures,[45] and one study reported improvement in "speech" (poorly specified) in a small number of severely impaired patients (≥3 months post-onset).[46]

Some pharmacological treatments are proposed to promote regeneration of damaged tissue by suppressing endogenous proteins associated with negative outcomes, such as Nogo-A, which limits the central nervous system's capacity for repair by inhibiting vascular growth and sprouting of neural processes following stroke. Findings from animal models suggest suboptimal potential for translation to language due to apparent reliance on contralesional structures, while the best recovery in humans is associated with a return to premorbid function (i.e., ipsilesional dominance).[47]

Various growth factors (neurotrophins) may also play a role in stroke recovery. Neurotrophins are endogenous substances that stimulate cellular proliferation and healing. While apparently lower in health, higher neurotrophin levels following stroke may be predictive of better recovery.[47] Therefore, drug treatment to increase neurotrophin levels may be beneficial, although the precise proteins to target are not yet established, and these may vary based on time since stroke or with specific deficits.

The genetic basis for aphasia recovery, whether in acute or chronic stages, is not understood. One study examining neurotrophin genotyping in chronic aphasia (specifically brain derived neurotrophic factor; BDNF) suggests that there may be an interaction between the allele one carries and tDCS response;[48] however, tDCS does not increase BDNF serum levels.[28] It is possible that further understanding of genetic influences on aphasia recovery, coupled with the advent of

tools for genotype modification (e.g., CRISPR), may ultimately create tenable intervention targets in the future.

CONCLUSIONS

This review of biological approaches to chronic aphasia likely raises more questions than it answers. In general, studies lack adequate samples and robust design, leaving a relatively small collection for evaluation. Yet if we envision aphasia treatment based on a medical model (focused on repair rather than compensation), intervention cannot continue to rely exclusively on the modest benefits offered by SLT. There is great potential for noninvasive brain stimulation and some pharmacological approaches, although further work is essential. In particular, studies need to employ more systematic approaches to explore the enormous parameter spaces these techniques offer.

While we sought to be comprehensive, many important areas were not addressed due to unavailability of data and constraints of space. These include neurological impacts of treatment, which may ultimately inform future intervention, and many important features of treatment response, such as lesion size/extent, aphasia type, and comorbidities. We were also unable to include behavioral SLT approaches developed with consideration of neurophysiology or principles of plasticity. Further, exercise and mind-body practices (e.g., meditation) may also influence brain function. Importantly, none of these studies address emotional and affective sequelae, key considerations in functional outcomes and quality of life in aphasia, which have been treated with the biological interventions described here in populations without aphasia. There remains much work to be done in this field.

There is strong potential for noninvasive brain stimulation, particularly tDCS, but this is hampered by inconsistent dosing, outcome measures, and maintenance periods, even from the same researchers, and effect sizes are generally modest. Other approaches, including TMS and pharmacotherapy (e.g., memantine, vasopressin), have limited studies with robust design but offer encouraging evidence for additional investigation. Regenerative/genetic therapies have a strong theoretical basis but no current empirical support. Critically, behavioral therapies paired with these approaches may be key to establishing effects, but these are often not applied or reported details are underspecified. Notably, the field most involved in aphasia treatment, speech-language pathology, cannot write prescriptions and may have limited collaborations with medical doctors and other professionals who can. It may also be the case that intervention combinations (e.g., drug + tES) will offer the greatest benefit, particularly accompanied by behavioral concomitants inducing experience-dependent plasticity, and all approaches may need tailoring on an individual basis (i.e., personalized medicine) to optimize outcomes. Still, this is an emerging field that provides promise for ultimately improving functional capacity and quality of life for those with aphasia.

We anticipate interest in such methods will continue and mature, ultimately developing an evidence base to support broader application in standard practice.

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Conflicts of interest

There are no conflicts of interest.

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