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BIOLOGICAL APPROACHES TO APHASIA TREATMENT

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Abstract

Herein, we review the basic mechanisms neural regeneration and repair and attempt to correlate the findings from animal models of stroke recovery to clinical trials for aphasia. Several randomized, controlled clinical trials that have involved manipulation of different neurotransmitter systems, including noradrenergic, dopaminergic, cholinergic and glutamatergic systems, have shown signals of efficacy. Biological approaches such as anti-Nogo and cell-replacement therapy have shown efficacy in preclinical models, but have yet to reach proof of concept in the clinic. Finally, noninvasive cortical stimulation techniques have been used in a few small trials, and have shown promising results. It appears that the efficacy of all of these platforms can be potentiated through coupling with speech-language therapy. Given this array of potential mechanisms that exist to augment and/or stimulate neural reorganization after stroke, we are optimistic that approaches to aphasia therapy will transition from compensatory models to models where brain reorganization is the goal.

INTRODUCTION

The ultimate goal of aphasia therapy should be the repair and reorganization of the injured brain. We advocate a medical model in which aphasia recovery directly reflects repair of neural circuits for language and associated cognitive functions, such as memory and attention. Many approaches to neural remediation have been proposed (e.g., sympathomimetics, neurotrophins, cell transplantation, or neural stimulation). It is important to note that the biological organism develops skill through interaction with the environment. For example, studies of pharmacological intervention for stroke rehabilitation have consistently shown that successful drug therapy is always accompanied by behavioral practice [1]. This finding is consistent with the well-established notion from synaptic physiology that plasticity is stimulus-driven patterns of neural activity [2], and is the theoretical foundation of constraint-induced movement therapy. Furthermore, when computational neural network models are experimentally damaged, by removing “neurons” or adding noise, restoring them to perform their original functions is not possible solely by replacing the lost “tissue”, but requires additional training [3,4]. These suggest that a combination of behavioral training and biological intervention can be used to effect the desired (direct or indirect) circuit changes.

In this paper, we review the biological basis of therapies directed at neural remediation in aphasia and the clinical literature evaluating these therapies. Since the pathophysiology of stroke in the acute phase is likely very different than that in the chronic phase, and since aphasia becomes a particular focus of patient concern in the later phases, we will focus on

modalities that influence the subacute or chronic phases of stroke. Patients in this stage of illness represent a tremendous unmet medical and societal need.

ANIMAL MODELS

Mechanisms of recovery and pharmacotherapy

The neural substrates of functional recovery from cortical lesions have been characterized in multiple systems and species. Several mechanisms have been described, and these include axonal sprouting, elaboration of dendritic spines, migration of subventricular stem cells to the infarction zone, or modulation of the strength or excitability of existing synapses. These mechanisms operate on different spatial and temporal scales and are differentially suited to compensate for different types of lesions and different phases of recovery. Since such mechanisms are likely to be differentially sensitive to pharmacological manipulation, one might postulate that different etiological or anatomical forms of infarction would require different forms of intervention.

Catecholamine-based therapy

Catecholamines are a natural target for stroke therapeutics given the alterations in catecholamine levels surrounding ischemic lesions [5], and given that pharmacological antagonism of adrenergic receptors delays spontaneous recovery from cortical damage [6]. A number of mechanisms are postulated to underlie the beneficial effects of catecholamine enhancement, including alteration of expression of synaptic proteins [7], enhancing neural regeneration [8], or altering synaptic strength [9]. These studies suggest that catecholamine augmentation may affect neuronal plasticity on multiple temporal and spatial scales.

Early work demonstrated that administration of a single dose of D-amphetamine, interacting synergistically with physical activity, can facilitate recovery of beam walking behavior after ablation of motor cortex [10]. This basic finding has been reproduced in several models of cortical damage [11,12]. The effect of D-amphetamine on motor recovery can be blocked by haloperidol [10], a D2 antagonist, with weaker antagonism at the alpha1 adrenoreceptor). Further, intraventricular norepinephrine, but not dopamine, reproduces the beneficial effect of D-amphetamine [13]. These, coupled with the finding that alpha1 receptor blockade impairs spontaneous recovery [6], indicate that norepinephrine acting on alpha-1 adrenergic receptors is the primary driver of functional recovery in these models. However, it has been suggested, based primarily on data from levodopa-enhanced word-list learning in normal humans, and the low rates of conversion of levodopa to norepinephrine (~5%), that dopamine plays a more dominant role [14]. As will be described below, the mixed clinical picture surrounding drugs like amphetamine and levodopa, which activate multiple receptor types, suggests that there is a need to define more precisely the mechanism of action of these drugs.

Cholinergic mechanisms

Acetylcholine (ACh) is thought to be involved in a number of aspects of cognition, including perception, selective attention, associative learning, and memory. Evidence for the potential for ACh-augmentation as a therapeutic modality to enhance plasticity is derived from findings in the auditory cortex, where experience-dependent alterations of sensory maps was greatly enhanced when sensory stimulation was coupled with stimulation of cholinergic fibers from the basal forebrain [15]. Notably, map reorganization parameters were directly related to the specific training stimuli used, emphasizing the importance of the interactions between specific behavioral therapy and pharmacologic intervention. One view is that ACh neurons serve a modulatory function in marking important stimuli [15]. This experience- and acetylcholine-dependent map reorganization learning is probably mediated by

muscarinic cholinergic receptors, rather than nicotinic receptors, since this learning can be blocked by scopolamine, a muscarinic antagonist [16].

Serotonin and Brain-Derived Neurotrophic Factor

Serotonin (5HT) has been shown to facilitate some forms of cortical map reorganization [17], and regeneration of hippocampal cells [18], though there is meager evidence supporting a role for 5HT in promoting neural reorganization in the chronic stroke setting. More attention has been paid to the ability of 5HT to enhance the expression of brain-derived neurotrophic factor (BDNF). Rodent studies have shown that inhibition of BDNF using antisense oligonucleotides impairs functional recovery from motor cortex stroke [19]. Other rodent work has demonstrated that exogenous BDNF facilitates motor recovery from acute stroke, without reducing infarct size, [20]. The latter point is important because it helps to disentangle neuroprotective effects of the approach (which have so far not been proven to be translatable for any drug) from effects that are mediated via neural reorganization. Despite these encouraging findings, there are major hurdles to the translation of this therapy to the clinic. Drug delivery of such a large molecule to the CNS poses a problem, particularly in the chronic phase of stroke when the blood-brain barrier has reconstituted. Drugs that enhance 5HT release may circumvent this problem by indirectly increasing BDNF levels. However, SSRI studies in chronic stroke have had a mixed track record in terms of motor recovery [21,22].

Extracellular matrix-based mechanisms

Stroke induces the expression of a number of extracellular molecules that are potentially hostile to axonal outgrowth. Among these, the Nogo-A system has been the best characterized, and inhibitors of this system have resulted in enhanced recovery of motor function in several studies [10,22]. Of potential relevance for the therapy of aphasia is the finding from one of these studies that intraventricular administration of anti-Nogo antibodies promoted recovery in a rodent model of hemispatial neglect [23]. No animal studies of anti-Nogo therapy, to our knowledge, have been done in the late chronic phase of stroke. However, since the studies referenced above have not demonstrated any alteration in infarct size after anti-Nogo therapy, anti-Nogo therapy may promote neural reorganization, rather neuronal protection.

Cell-based mechanisms

Multiple approaches have emerged to either promote proliferation and/or differentiation endogenous neural stem cells after stroke or to provide exogenous sources of pluripotent cells to replace portions of damaged circuits. Early clinical studies that examined the feasibility of direct transplantation of either human immortalized human neural cells [24], autologous mesenchymal stem cells [25], fetal porcine cells [26], or G-CSF administration [27] were of small size and unclear efficacy, but established the feasibility of this approach. More recent work has focused on less immunologically active cell types and less invasive delivery systems. Autologously derived mesenchymal cells or CD34+ peripheral blood cells (both are pluripotent) have been shown to promote stroke recovery in both the acute phase [28] and subacute/chronic phase [29]. It is notable that, similar to small-molecule therapy, there is a beneficial interaction between physical activity and the biological therapy [30].

PHARMACOTHERAPY OF APHASIA

In our view, the optimum study design to establish that a pharmacological agent promotes brain reorganization to enhance language processing would be a double-blind, placebo-controlled, adequately-powered, parallel-group study that contains at least one outcome measure that is assessed after drug washout to ensure that any benefit observed is not only

due to temporary enhancement of arousal. Unfortunately, very few studies have had this type of design. Table 1 contains a partial list of the drugs that have been used in aphasia clinical trials. There have been 17 prospective, double blind studies on patients with subchronic or chronic stroke that assessed language as a primary outcome measure.

Noradrenergic agents

Four prospective, placebo-controlled, double blind studies examined the effects of either D-amphetamine or methylphenidate on language function in aphasic patients. The largest and most frequently cited study is that by Walker-Batson et al. [31]. In this study, a greater percentage of subjects receiving D-amphetamine + SLT demonstrated an improvement on the Porch Index of Communicative Ability (PICA) scale than their placebo + SLT counterparts at the 6 week time point (83% vs. 22%), which was assessed one-week after last dose of drug. There was a nonsignificant trend for a persistent benefit at 6 months after dosing. Unfortunately, this study was confounded by differences in the amount of therapy received (D-amphetamine patients received 21% more therapy time), and by the lack of screening for depression. A more recent study by Whiting et al. [32], using a single-cohort design in two chronic aphasics, also demonstrated improvements in naming associated with D-amphetamine. These two small studies both have serious design flaws, but arouse interest in the use of D-amphetamine, coupled with speech and language therapy (SLT), for chronic aphasia. Two earlier placebo-controlled studies did not show a benefit of D-amphetamine therapy [33,34].

D-amphetamine coupled with SLT has also been shown to improve language performance and alter the activation of language-related networks in the brain. Breitenstein et al. [35] taught healthy subjects an artificial vocabulary and coupled this training with D-amphetamine. They found that D-amphetamine enhanced learning of the artificial words, and that this difference persisted one month post-drug. In addition, Ufring et al. [36] demonstrated that amphetamine specifically increased activation in auditory cortical regions during tone discrimination tasks, and enhanced activation of motor cortical areas during motor tasks. Sommer et al. [37] found that D-amphetamine administration during verb generation and semantic decision increased overall left hemispheric activation, and increased activation of both inferior frontal gyri and the left supramarginal gyrus, and did not significantly increase activation of multiple other volumes of interest. These data suggest that D-amphetamine can act to potentiate activity and plasticity of behaviorally activated networks, rather than in a non-specific fashion. Note that these studies all suggest that sympathomimetics play an adjunctive role to behavioral or physical therapy, rather than as a primary treatment.

It is important to note that after early promising small trials, D-amphetamine has failed to show benefit in several recent well-designed, appropriately powered trials of recovery of motor function after stroke [38,39]. It is difficult to predict whether D-amphetamine for aphasia will meet a similar fate, but the absence of a proof of concept in analogous stroke models should provide a note of caution for the use of D-amphetamine therapy.

Though most of the literature has been directed towards the investigation of the benefits of sympathomimetic compounds, an additional report documented the effect of propranolol, a beta1/beta2 adrenergic antagonist, on language function [40]. In this study, 4 chronic Broca's aphasic patients were given single doses of propranolol or placebo and had language assessed via performance the Boston Naming Test across three separate drug trials. The authors found consistent small increases in naming performance (average BNT before drug = 26.3, after drug = 29.0). The authors speculate that the benefits of beta antagonism may be related to suppression of background activity.

Dopamine Agonists and L-Dopa

Bragoni et al. [41] studied the effects of high-dose bromocriptine (up to 30 mg TID) on chronic non-fluent aphasics in a single-cohort study. They found that bromocriptine + SLT for 60 days improved performance on several language metrics over SLT alone. There was a trend for benefit to be sustained after a 60-day washout period. A more recent study by Seniow et al [42] utilized a parallel design of 39 patients with subacute stroke, randomized to receive either 100 mg L-dopa or placebo. Drug therapy was timed to precede 5x/weekly SLT by 30 minutes, and continued for three weeks. The Boston Diagnostic Aphasia Examination (BDAE) was used as the primary outcome measure. They found improvement on all metrics, but this only reached statistical significance for verbal fluency, repetition of phrases and sentences and repetition of words. Washout performance was not assessed. Several studies of dopamine-based therapy did not show efficacy. Ashtary et al. [43] examined the impact of bromocriptine, started during the acute phase and continued for 4 months and found no benefit to bromocriptine administration on a standardized Persian language test. It is not clear if any of the subjects received SLT. Two more crossover studies, neither of which required SLT, also did not show efficacy for bromocriptine [44] [45]

It is notable that the two studies that demonstrated efficacy for dopamine therapy explicitly coupled dopamine therapy to SLT, while the three studies that did not show efficacy had no requirement for SLT. This is consistent with the animal literature described previously. These data are also consistent with much of the data from the motor recovery literature, where L-Dopa, when coupled with physical therapy, has improved motor outcomes [46,47]. The totality of the data, then, suggests that bromocriptine or L-dopa therapy, coupled with SLT, holds promise for aphasia treatment.

Cholinergics and Anticholinergics

There have been relatively few attempts to modulate the cholinergic system for the treatment of aphasia. Inhibitors of acetylcholinesterase are in widespread use for Alzheimer's disease, and in general, have good safety and tolerability. In a randomized controlled-trial, Berthier et al. [48] found that chronic aphasic patients receiving 16 weeks of donepezil improved significantly on the Western Aphasia Battery, the Communicative Activity Log and the picture naming subtest of the Psycholinguistic Assessment of Language Processing in Aphasia test. The improvements noted at week 16 were not present at week 20, suggesting that the benefits of donepezil are not related to neural reorganization. This lack of persistent benefit is similar to what has been seen in Alzheimer's Disease..

Piracetam

Piracetam has multiple loci of CNS activity. It facilitates cholinergic and excitatory amine neurotransmission, increases regional cerebral blood flow and alters neuronal membrane properties [49]. It is not clear which of its biological effects are responsible for the purported cognitive benefit. It is currently available as a nutritional supplement in the U.S. and is approved for the treatment of myoclonus in Europe.

In post-acute and chronic aphasia, one randomized controlled trial showed significant improvement on a multivariate analysis of Aachen Aphasia subtest scores relative to baseline in favor of piracetam ($p = 0.02$) at 12 weeks. This effect was no longer present at 24 weeks [50]. A later double-blind, placebo-controlled study in chronic aphasia showed improvement on a single subtest of the AAT (written language) [51]. Integrating functional neurological measures into a treatment trial, another study showed an increase of activation in several left hemisphere language regions over the course of treatment, more in the

treatment group than the placebo group. The piracetam group improved on six language measures, the placebo group on three [52].

Memantine

Memantine is a noncompetitive NMDA receptor antagonist, approved for the treatment of moderate to severe Alzheimer's disease. A single trial has been performed that examined the efficacy of memantine to treat chronic aphasia due to stroke. Berthier et al. [53] found that 20 mg daily of memantine for 16 weeks, in the absence of SLT, produced enhanced performance on the Western Aphasia Battery. Incorporation of constraint-induced aphasia therapy for 2 weeks produced further separation of the memantine group from the placebo group. After a 4-week washout, the memantine group's WAB performance declined substantially, but was slightly better than the placebo group ($p = 0.041$). This study is suggestive of an effect of memantine in the absence of SLT, although evidence for a synergistic relationship between CIAT and memantine is weakened by the differences in Western Aphasia Battery scores at the onset of CIAT. Given the good efficacy and tolerability profile of combination use of donepezil and memantine for Alzheimer's Disease, the positive studies for both drugs and aphasia described here, it would be interesting to examine the effects of combination therapy on aphasia recovery.

Vasopressin

Vasopressin can act at multiple brain regions and is thought to be important in mediating social behavior [54] as well as multiple cognitive domains. Tsikunov and Belowkoskova [55] examined the effects of intranasal desmopressin (a V1b-V2-receptor agonist) administration in patients with chronic stroke-related aphasia and observed "good" responses (improvements on at least 3 out of 10 language tests) in 13/26 subjects. SLT was not incorporated into this trial. One intriguing factor here is the literature supporting V1 agonism and social behavior [54]. It would be interesting to determine if the language benefits of desmopressin are driven by alterations in social behavior.

OTHER BIOLOGICAL INTERVENTIONS

Transcranial Magnetic and Direct Current Stimulation

Transcranial magnetic (TMS) and DC (tDCS) electrical stimulation are noninvasive brain stimulation techniques that modulate cortical excitability. There is increasing evidence that these techniques can enhance the effect of training on performance of certain motor tasks, as well as some other cognitive tasks such as aphasia [56]. These approaches provide a significant amount of flexibility to be combined with other therapeutic modalities. A relatively straightforward approach would be to use high-frequency TMS (thought to increase cortical excitability) to activate hypoactive networks. This approach was used by Cotelli et al. to acutely improve the naming ability of Alzheimer's Disease patients via stimulation of the dorsolateral prefrontal cortex [57]. Another approach is to use low-frequency TMS (thought to induce inhibition) to quiet pathologically hyperactive brain regions (the language equivalent of the "Sprague Effect"). For example, based on the hypothesis that contralesional activation in aphasic patients is detrimental to language outcome, Naeser et al. used slow repetitive TMS to inhibit the anterior portion of the right-sided homolog of Broca's area in aphasic patients. They reported long-lasting improvements in naming in 4 patients with Broca-type aphasia in an open-label study [58]. Stimulation approaches can also be incorporated into behavioral paradigms. Floel et al. used tDCS over the left peri-Sylvian areas while normal subjects were taught a foreign lexicon and found that subjects receiving anodal stimulation had enhanced naming accuracy relative to their sham counterparts [59]. Finally, stimulation approaches may enhance traditional therapeutic approaches post-stroke. Hesse et al. combined tDCS with robot-assisted arm training in

patients with motor deficits in an uncontrolled pilot study. Interestingly, they found that 4 out of the 5 aphasic patients in their sample improved on the Aachen Aphasia Test [60]. Clearly, brain stimulation approaches are in their earliest stages, and the studies cited above are small and preliminary. However, the relative ease of implementation of these approaches and their high safety margins suggest that their use will increase over time. One interesting possibility is that directed brain stimulation techniques may become a surrogate for physical or speech therapy in patients unable to actively participate in traditional approaches.

Tissue Transplantation

There have been few completed studies utilizing cell-based, or growth factor-based therapy for stroke, and none of these studies have looked at aphasic patients. Based on registration on clinicaltrials.gov, there are currently at least active 5 trials that involve the intravenous infusion of several types of autologous sources of stem cells for acute ischemic stroke, at least 5 trials that examine the effects of erythropoietin and at least two studies examining the effects of G-CSF analogs in acute ischemic stroke. Clearly, the next several years will bring a plethora of new data regarding the potential to stimulate the regeneration of lost circuits via cell- or growth-factor based therapy. Unfortunately, none of the ongoing studies are recruiting subjects in the chronic phases of stroke. It bears pointing out that the biological issues during the acute and chronic phases of stroke are quite different, and it should not be assumed that the efficacy, or lack thereof, in the current cohort of studies, will necessarily be predictive of efficacy for chronic stroke patients.

Avoiding Adverse Agents

Although the ultimate goal is to intervene biologically to potentiate language learning, communication, and cerebral plasticity, one biological intervention that is possible today, and could have enormous benefit, is to withhold interventions that could have negative effects on these processes. Drugs that can adversely affect aphasia recovery include agents used to treat a number of highly prevalent diseases, particularly in aphasic patients, namely, hypertension, coronary artery disease, seizures, anxiety, psychotic symptoms, and gastrointestinal disturbances. A selection of drugs with probable deleterious effects on aphasia are shown in Table 2. General classes of drugs that are most notable in this regard are alpha-adrenergic antagonist, GABA-potentiators, drugs with anti-cholinergic side effects and anti-seizure medications, particularly topiramate (most common offender), phenytoin and vigabatrin [61–63].

This work has profound relevance to aphasia rehabilitation as it is currently practiced, independent of the explicit biological interventions discussed here. In order to maximize functional recovery, it is important not only to ensure adequate behavioral treatment, but also to ensure the appropriate neurobiological substrate for this treatment. It is thus advisable for patients in aphasia therapy to avoid drugs that might interfere with catecholaminergic, cholinergic or GABAergic function, or are thought to delay recovery by empirical study.

SUMMARY AND CONCLUSIONS

There are increasingly reliable data suggesting a potential beneficial effect potentiation of catecholaminergic, particularly dopaminergic, transmission on aphasia rehabilitation. The data are also promising for drugs that potentiate acetylcholine, as well as for compounds where the scientific rationale and mechanisms are less clear, such as memantine, piracetam and vasopressin. No trials using cell-based or other biological agents have been performed that used language metrics as primary outcome measures. The non-aphasic stroke literature for these therapies has yet to reach the proof-of-concept stage, so it is impossible to

speculate regarding the potential impact of these therapies. It is important to note that despite some of the encouraging data in the aphasia trials, the effect sizes are generally small, and there are very little data demonstrating an impact of drug therapy on quality of life or functional outcome measures. Further, despite the common practice in most chronic diseases of multi-drug therapy to attack different pathophysiological pathways, there have been no randomized trials of combination therapy for aphasic stroke therapy. In addition, different etiological forms of aphasia probably have different natural histories and therefore different sensitivities to pharmacotherapy, and this has not yet been explored. Larger multi-center studies of these questions are needed.

In most cases, drug efficacy has only been seen when coupled with active SLT, which was strongly predicted by the animal literature. Indeed, SLT is likely the “behavioral engine” that drives pharmacological responses [64]. Therefore, neither pharmacotherapy nor stimulation methods should be used as a substitute for speech and language therapy. In addition, it is likely that different forms of drug therapy are likely to interact optimally with different forms of SLT, and this should be explored.

It is very likely that pharmacotherapy and stimulation devices will ultimately play a valuable role as an adjunct to behavioral rehabilitation to speed recovery, improve learning, decrease performance variability, and improve mean performance in patients with mild to moderate language dysfunction from cerebral infarctions.

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References

1. Small, SL. Biological Approaches to the Treatment of Aphasia. In: Hillis, A., editor. *Handbook on Adult Language Disorders: Integrating Cognitive Neuropsychology, Neurology, and Rehabilitation*. Psychology Press; Philadelphia, Pennsylvania: 2001. p. 397-411.
2. Horng S, Sur M. Visual activity and cortical rewiring: activity-dependent plasticity of cortical networks. *Progress in Brain Research*. 2006; 157:3–11. [PubMed: 17167899]
3. McCloskey, M.; Cohen, NJ. Catastrophic Interference in Connectionist Networks: The Sequential Learning Problem. In: Bower, G., editor. *The Psychology of Learning and Motivation*. Academic Press; New York: 1989. p. 109-165.
4. Gernsbacher, MA.; St John, MF. Learning and losing syntax: Practice makes perfect and frequency builds fortitude. In: Healy, AF.; Bourne, JLE., editors. *Foreign language learning: Psycholinguistic experiments on training and retention*. Laurence Erlbaum Associates; Mahwah, NJ: 1998. p. 231-255.
5. Cohen HP, Woltz AG, Jacobson RL. Catecholamine Content of Cerebral Tissue after Occlusion or Manipulation of Middle Cerebral Artery in Cats. *Journal of Neurosurgery*. 1975; 43:32–36. [PubMed: 1141982]
6. Feeney D, Westerberg V. Norepinephrine and brain damage: alpha noradrenergic pharmacology alters functional recovery after cortical trauma. 1990; 2:44.
7. Stroemer RP, Kent TA, Hulsebosch CE. Neocortical neural sprouting, synaptogenesis, and behavioral recovery after neocortical infarction in rats. *Stroke*. 1995; 26:2135–44. [PubMed: 7482662]
8. Hiramoto T, Ihara Y, Watanabe Y. [alpha]-1 Adrenergic receptors stimulation induces the proliferation of neural progenitor cells in vitro. *Neuroscience Letters*. 2006; 408:25–28. [PubMed: 16989945]
9. Izumi Y, Zorumski C. Norepinephrine promotes long-term potentiation in the adult rat hippocampus in vitro. *Synapse*. 1999; 31:196–202. [PubMed: 10029237]

10. Feeney D, Gonzalez A, Law W. Amphetamine, Haloperidol, and Experience Interact to Affect Rate of Recovery After Motor Cortex Injury. *Science*. 1982; 217:855–857. [PubMed: 7100929]
11. Papadopoulos CM, et al. Motor Recovery and Axonal Plasticity With Short-Term Amphetamine After Stroke. *Stroke*. 2009; 40:294–302. [PubMed: 19038917]
12. Ramic M, et al. Axonal plasticity is associated with motor recovery following amphetamine treatment combined with rehabilitation after brain injury in the adult rat. *Brain Research*. 2006; 1111:176–186. [PubMed: 16920088]
13. Boyeson, MG.; Feeney, DM. The Role of Norepinephrine in Recovery from Brain Injury (abstract). Annual Meeting of the Society for Neuroscience; 1984.
14. Breitenstein C, et al. A shift of paradigm: From noradrenergic to dopaminergic modulation of learning? *Journal of the Neurological Sciences*. 2006; 248:42–47. [PubMed: 16815467]
15. Kilgard MP, Merzenich MM. Cortical map reorganization enabled by nucleus basalis activity. *Science*. 1998; 279:1714–8. [PubMed: 9497289]
16. Thiel CM, Friston KJ, Dolan RJ. Cholinergic Modulation of Experience-Dependent Plasticity in Human Auditory Cortex. *Neuron*. 2002; 35:567–574. [PubMed: 12165477]
17. Gu Q, Singer W. Involvement of serotonin in developmental plasticity of kitten visual cortex. *European Journal of Neuroscience*. 1995; 7:1146–1153. [PubMed: 7582087]
18. Li WL, et al. Chronic fluoxetine treatment improves ischemia-induced spatial cognitive deficits through increasing hippocampal neurogenesis after stroke. *Journal of Neuroscience Research*. 2009; 87:112–122. [PubMed: 18711744]
19. Ploughman M, et al. Brain-Derived Neurotrophic Factor Contributes to Recovery of Skilled Reaching After Focal Ischemia in Rats. *Stroke*. 2009; 40:1490–1495. [PubMed: 19164786]
- 20. Schabitz W-R, et al. Intravenous Brain-Derived Neurotrophic Factor Enhances Poststroke Sensorimotor Recovery and Stimulates Neurogenesis. *Stroke*. 2007; 38:2165–2172. This study established preclinical proof-of-concept for the peripheral administration of BDNF, a large molecule which crosses the blood-brain barrier in rats. Importantly, this study employed non-neuroprotective doses of BDNF, which will be an important point in the design of studies of agents that have both neural protective properties and have the ability to promote neural reorganization. [PubMed: 17510456]
21. Boyeson M, Harmon R, Jones J. Comparative effects of fluoxetine, amitriptyline and serotonin on functional motor recovery after sensorimotor cortex injury. *Am J Phys Med Rehabil*. 1994; 73:76–83. [PubMed: 8148107]
22. Windle V, Corbett D. Fluoxetine and recovery of motor function after focal ischemia in rats. *Brain Research*. 2005; 1044:25–32. [PubMed: 15862786]
- 23. Brenneman MM, et al. Nogo-A inhibition induces recovery from neglect in rats. *Behavioural Brain Research*. 2008; 187:262–272. This is the only study, to our knowledge, that has induced recovery, and tracked the mechanism of that recovery, in an animal cognitive model. The latter point is important since it provides a benchmark with which to evaluate the therapy in clinical trials. If one cannot show via sensitive tools (such as fMRI) that anti-Nogo therapy in neglect subjects can enhance contralesional activity, the likelihood is low that one would observe benefits using more traditional (but less sensitive) outcome measures. [PubMed: 17963852]
24. Kondziolka D, et al. Transplantation of cultured human neuronal cells for patients with stroke. *Neurology*. 2000; 55:565–9. [PubMed: 10953194]
25. Bang O, et al. Autologous mesenchymal stem cell transplantation in stroke patients. *Annals of Neurology*. 2005; 57:874–882. [PubMed: 15929052]
26. Savitz SI, et al. Neurotransplantation of Fetal Porcine Cells in Patients with Basal Ganglia Infarcts: A Preliminary Safety and Feasibility Study. *Cerebrovascular Diseases*. 2005; 20:101–107. [PubMed: 15976503]
27. Sprigg N, et al. Granulocyte-Colony-Stimulating Factor Mobilizes Bone Marrow Stem Cells in Patients With Subacute Ischemic Stroke: The Stem Cell Trial of Recovery Enhancement After Stroke (STEMS) Pilot Randomized, Controlled Trial (ISRCTN 16784092). *Stroke*. 2006; 37:2979–2983. [PubMed: 17082474]

28. Liu YP, et al. Neuroprotective effects of mesenchymal stem cells derived from human embryonic stem cells in transient focal cerebral ischemia in rats. *J Cereb Blood Flow Metab.* 2009; 29:780–791. [PubMed: 19209181]
29. Shyu WC, et al. Intracerebral Peripheral Blood Stem Cell (CD34+) Implantation Induces Neuroplasticity by Enhancing beta1 Integrin-Mediated Angiogenesis in Chronic Stroke Rats. *J Neurosci.* 2006; 26:3444–3453. [PubMed: 16571751]
30. Hicks AU, et al. Enriched environment enhances transplanted subventricular zone stem cell migration and functional recovery after stroke. *Neuroscience.* 2007; 146:31–40. [PubMed: 17320299]
31. Walker-Batson D, et al. A Double-Blind, Placebo-Controlled Study of the Use of Amphetamine in the Treatment of Aphasia Editorial Comment. *Stroke.* 2001; 32:2093–2098. [PubMed: 11546902]
32. Whiting E, et al. Dexamphetamine boosts naming treatment effects in chronic aphasia. *Journal of the International Neuropsychological Society.* 2007; 13:972–979. [PubMed: 17942015]
33. Darley F, Keith R, Sasanuma S. The Effect of Alerting and Tranquilizing Drugs Upon the Performance of Aphasic Patients. *Clinical Aphasiology.* 1977; 7:91–96.
34. McNeil MR, et al. A double-blind, placebo-controlled study of pharmacological and behavioral treatment of lexical-semantic deficits in aphasia. *Aphasiology.* 1997; 11:358–400.
35. Breitenstein C, et al. D-Amphetamine Boosts Language Learning Independent of its Cardiovascular and Motor Arousing Effects. *Neuropsychopharmacology.* 2004; 29:1704–1714. [PubMed: 15114342]
36. Uftiring S, et al. An fMRI study of the effect of amphetamine on brain activity. *Neuropsychopharmacology.* 2001; 25:925–35. [PubMed: 11750185]
37. Sommer I, et al. The influence of amphetamine on language activation: an fMRI study. *Psychopharmacology.* 2006; 183:387–393. [PubMed: 16284750]
38. Gladstone DJ, et al. Physiotherapy Coupled With Dextroamphetamine for Rehabilitation After Hemiparetic Stroke: A Randomized, Double-Blind, Placebo-Controlled Trial. *Stroke.* 2006; 37:179–185. [PubMed: 16322487]
39. Platz T, et al. Amphetamine fails to facilitate motor performance and to enhance motor recovery among stroke patients with mild arm paresis: interim analysis and termination of a double blind, randomised, placebo-controlled trial. *Restor Neurol Neurosci.* 2005; 23:271–80. [PubMed: 16477089]
40. Beversdorf DQ, et al. Effect of Propranolol on Naming in Chronic Broca's Aphasia with Anomia. *Neurocase: The Neural Basis of Cognition.* 2007; 13:256–259.
41. Bragoni M, et al. Bromocriptine and speech therapy in non-fluent chronic aphasia after stroke. *Neurol Sci.* 2000; 21:19–22. [PubMed: 10938198]
42. Seniów J, et al. 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. *Journal of the Neurological Sciences.* 2009 In Press, Corrected Proof.
43. Ashtary F, et al. A randomized, double-blind trial of bromocriptine efficacy in nonfluent aphasia after stroke. *Neurology.* 2006; 66:914–916. [PubMed: 16567711]
44. Sabe L, et al. A randomized, double-blind, placebo-controlled study of bromocriptine in nonfluent aphasia. *Neurology.* 1995; 45:2272–2274. [PubMed: 8848206]
45. Gupta S, et al. Bromocriptine treatment of nonfluent aphasia. *Neurology.* 1995; 45:2170–3. [PubMed: 8848187]
46. Rösser N, et al. Levodopa Improves Procedural Motor Learning in Chronic Stroke Patients. *Archives of Physical Medicine and Rehabilitation.* 2008; 89:1633–1641. [PubMed: 18760148]
47. Scheidtmann K, et al. Effect of levodopa in combination with physiotherapy on functional motor recovery after stroke: a prospective, randomised, double-blind study. *The Lancet.* 2001; 358:787–790.
- 48. Berthier ML, et al. A randomized, placebo-controlled study of donepezil in poststroke aphasia. *Neurology.* 2006; 67:1687–1689. This is a well-designed study that demonstrates the efficacy of donepezil to improve language performance in chronic aphasics. This study avoided some of the problems of previous aphasia therapy trials, such that there the study groups were well-balanced,

the study had adequate power, had specified primary and secondary outcome measures, and assessed the effects of drug at washout. [PubMed: 17101908]

49. Müller W, Eckert G, Eckert A. Piracetam: novelty in a unique mode of action. *Pharmacopsychiatry*. 1999; 32:2–9. [PubMed: 10338102]
50. Enderby P, et al. Effect of piracetam on recovery and rehabilitation after stroke: a double-blind, placebo-controlled study. *Clin Neuropharmacol*. 1994; 17:320–31. [PubMed: 9316679]
51. Huber W, et al. Piracetam as an adjuvant to language therapy for aphasia: a randomized double-blind placebo-controlled pilot study. *Arch Phys Med Rehabil*. 1997; 78:245–50. [PubMed: 9084344]
52. Kessler J, et al. Piracetam improves activated blood flow and facilitates rehabilitation of poststroke aphasic patients. *Stroke*. 2000; 31:2112–6. [PubMed: 10978039]
53. Berthier M, et al. Memantine and constraint-induced aphasia therapy in chronic poststroke aphasia. *Annals of Neurology*. 2009; 65:577–585. [PubMed: 19475666]
54. Donaldson Z, Young L. Oxytocin, vasopressin, and the neurogenetics of sociality. *Science*. 2008; 322:900–4. [PubMed: 18988842]
55. Tsikunov SG, Belokoskova SG. Psychophysiological analysis of the influence of vasopressin on speech in patients with post-stroke aphasia. *The Spanish journal of psychology*. 2007; 10:178–88. [PubMed: 17549891]
- 56. Devlin JT, Watkins KE. Stimulating language: insights from TMS. *Brain*. 2007; 130:610–622. Well-written overview of the use of TMS both as an investigational tool as well as a potential therapeutic modality for aphasia. The authors provide both historical insight to the development of the technology and describe how the clever use of TMS has led to a greater understanding of the interactions between the motor system and speech perception. In addition, the authors review the theoretical rationale for right-sided TMS for aphasia and provide the context to interpret some of the early findings in the field. [PubMed: 17138570]
57. Cotelli M, et al. Transcranial magnetic stimulation improves naming in Alzheimer disease patients at different stages of cognitive decline. *European Journal of Neurology*. 2008; 15:1286–1292. [PubMed: 19049544]
58. Naeser MA, et al. Improved picture naming in chronic aphasia after TMS to part of right Broca's area: An open-protocol study. *Brain and Language*. 2005; 93:95–105. [PubMed: 15766771]
59. Floel A, et al. Noninvasive Brain Stimulation Improves Language Learning. *Journal of Cognitive Neuroscience*. 2008; 20:1415–1422. [PubMed: 18303984]
60. Hesse S, et al. Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: A pilot study. *Restorative Neurology and Neuroscience*. 2007; 25:9–15. [PubMed: 17473391]
61. Gil R, Neau JP. Rapid aggravation of aphasia by vigabatrin. *J Neurol*. 1995; 242:251–2. [PubMed: 7798126]
62. Kennedy G, Lhatoo S. CNS adverse events associated with antiepileptic drugs. *CNS Drugs*. 2008; 22:739–60. [PubMed: 18698874]
63. Mula M, et al. Topiramate and word-finding difficulties in patients with epilepsy. *Neurology*. 2003; 60:1104–7. [PubMed: 12682314]
- 64. Nadeau S, Wu S. CIMT as a behavioral engine in research on physiological adjuvants to neurorehabilitation: the challenge of merging animal and human research. *Neurorehabilitation*. 2006; 21:107–30. This review describes the rationale behind the coupling of physical therapy (particularly constraint-induced movement therapy) with drug or electrical stimulation therapy, and they describe their own groups' experiences with this approach. The authors also discuss practical issues such as translational strategies from the animal data and the incorporation of behavioral therapy into trial design. Overall, this review provides an excellent framework to implement multimodal approaches in clinical trials for chronic stroke. [PubMed: 16917158]

Table 1

Pharmacological agents investigated for use in aphasia therapy (partial list)

Amantidine
Amobarbital
Bifemelane
Bromocriptine
Chlordiazepoxide
Desmopressin
Dextro-amphetamine
Donepezil
Hyperbaric O ₂
Levodopa
Memantine
Meprobamate
Methylphenidate
Piracetam
Propranolol
Zolpidem

Table 2

Drugs with potentially deleterious effects on aphasia recovery

Specific Drug or Class of Agent	Reason for Administration	Neurotransmitter System
Benzodiazepines (e.g., Diazepam, Chlordiazepoxide, Lorazepam)	Anxiety	γ aminobutyric acid (GABA) agonist
Clonidine	Hypertension	α_2 adrenergic agonist
Labetalol (predominantly β -blocking but also α_1 antagonist)	Hypertension, Coronary artery disease	Partial α_1 adrenergic antagonist
Phenoxybenzamine, prazosin	Hypertension	α_1 adrenergic antagonist
Butyrphenones (e.g., Haloperidol), phenothiazines (e.g., Chlorpromazine), and related agents (e.g., Quetiapine)	Psychosis	D ₂ dopaminergic antagonist
Butyrphenones (e.g., Droperidol) and phenothiazines (e.g., Metaclopramide)	Gastrointestinal disturbances	D ₂ dopaminergic antagonist
Barbiturates (e.g., Phenobarbital)	Seizures	γ aminobutyric acid (GABA) agonist
Phenytoin	Seizures	Not transmitter specific
Topiramate	Seizures, Migraine	Glutamate, GABA, possibly others