Biological Approaches to Aphasia Treatment

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In this review, we discuss the basic mechanisms of neural regeneration and repair and attempt to correlate findings from animal models of stroke recovery with clinical trials for aphasia. Several randomized controlled clinical trials involving 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 these platforms can be potentiated through coupling with concomitant behavioral intervention. 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 in which 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 (eg, sympathomimetics, neurotrophins, cell transplantation, and neural stimulation). However, the biological organism develops skill through interaction with the environment, thus biological intervention alone might not suffice. In fact, studies of pharmacologic 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 dependent [2]. 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 findings suggest that a combination of behavioral training and biological intervention can be used to effect the desired (direct or indirect) circuit changes.

In this article, we review the biological basis of therapies directed at neural remediation in aphasia and the clinical literature evaluating these therapies. Because the pathophysiology of stroke in the acute phase likely is very different from that in the chronic phase, and because aphasia becomes a particular focus of patient concern in the later phases, we 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, including axonal sprouting, elaboration of dendritic spines, migration of subventricular stem cells to the infarction zone, and 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. Because such mechanisms likely are differentially sensitive to pharmacologic manipulation, one might postulate that different etiologic or anatomic 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 pharmacologic antagonism of adrenergic receptors delays spontaneous recovery from cortical damage [6]. Several mechanisms are postulated to underlie the beneficial

effects of catecholamine enhancement, including alteration of expression of synaptic proteins [7], enhancement of neural regeneration [8], and alteration of 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 dextroamphetamine (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 (a D_2 antagonist with weaker antagonism at the α_1 adrenoreceptor) [10]. Further, intraventricular norepinephrine, but not dopamine, reproduces the beneficial effect of D-amphetamine [13]. These, coupled with the finding that α_1 receptor blockade impairs spontaneous recovery [6], indicate that norepinephrine acting on α_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 in vivo (~ 5%), that dopamine plays a more dominant role [14]. As described later, the mixed clinical picture surrounding drugs such as amphetamine and levodopa, which activate multiple receptor types, suggests there is a need to define the mechanism of action of these drugs more precisely.

Cholinergic mechanisms

Acetylcholine (ACh) is thought to be involved in several 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, in which experience-dependent alterations of sensory maps were 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 ACh-dependent map reorganization learning is probably mediated by muscarinic cholinergic receptors rather than nicotinic receptors, as 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], although 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 disentangle the neuroprotective effects of the approach (which so far have not been proven to be translatable for any drug) from the effects 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 central nervous system 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, studies of selective serotonin reuptake inhibitors 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 several 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 [23]. 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 [24•]. No animal studies of anti-Nogo therapy, to our knowledge, have been done in the late chronic phase of stroke. However, because the aforementioned studies have not demonstrated any alteration in infarct size after anti-Nogo therapy, anti-Nogo therapy may promote neural reorganization rather than neuronal protection.

Cell-based mechanisms

Multiple approaches have emerged either to promote proliferation and/or differentiation of endogenous neural stem cells after stroke or to provide exogenous sources of pluripotent cells to replace portions of damaged circuits. Early clinical studies examining the feasibility of direct transplantation of immortalized human neural cells [25], autosomal mesenchymal stem cells [26], or fetal porcine cells [27], or administration of granulocyte colony-stimulating factor (G-CSF) [28], were small and of 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 of which are pluripotent) have been shown to promote stroke recovery in both the acute phase [29] and the subacute/chronic phase [30]. It is notable that, similar to small molecule therapy, there is a beneficial interaction between physical activity and the biological therapy [31].

Table 1. Pharmacologic agents investigated for use in aphasia therapy (partial list)

Amantadine
Amobarbital
Bifemelane
Bromocriptine
Chlordiazepoxide
Desmopressin
Dextroamphetamine
Donepezil
Hyperbaric O_2
Levodopa
Memantine
Meprobamate
Methylphenidate
Piracetam
Propranolol
Zolpidem

Pharmacotherapy of Aphasia

In our view, the optimum study design to establish that a pharmacologic agent promotes brain reorganization to enhance language processing is a double-blind, placebo-controlled, adequately powered, parallel-group study containing at least one outcome measure assessed after drug washout to ensure that any benefit observed is not just the result of 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 in 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 D-amphetamine or methylphenidate on language function in aphasic patients. The largest and most frequently cited study is the one by Walker-Batson et al. [32]. In this study, a greater percentage of subjects receiving D-amphetamine plus speech and language therapy (SLT) demonstrated an improvement on the Porch Index of Communicative Ability scale than their placebo-plus-SLT counterparts at the 6-week time point (83% vs 22%), which was assessed 1 week after the 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. [33] using a single-cohort design in two patients with chronic aphasia also demonstrated improvements in naming associated with D-amphetamine. Although these two small studies have serious design flaws, they have aroused interest in the use of D-amphetamine, coupled with SLT, for chronic aphasia. Two earlier placebo-controlled studies did not show a benefit from D-amphetamine therapy [34,35].

D-amphetamine coupled with SLT also has been shown to improve language performance and to alter the activation of language-related networks in the brain. Breitenstein et al. [36] 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 1 month post-drug. In addition, Uftring et al. [37] 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. [38] found that D-amphetamine administration during verb generation and semantic decision increased overall left hemispheric activation and activation of both inferior frontal gyri and the left supramarginal gyrus, but 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 acting in a nonspecific fashion. Note that these studies all suggest that sympathomimetics play an adjunctive role in behavioral or physical therapy, rather than as a primary treatment.

It is important to note that after early, promising small trials, D-amphetamine failed to show benefit in several recent well-designed, appropriately powered trials of recovery of motor function after stroke [39,40]. 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 provides a note of caution regarding the use of D-amphetamine therapy.

Although most of the literature has been directed toward the investigation of the benefits of sympathomimetic compounds, an additional report documented the effect of propranolol, a β_1/ β_2-adrenergic antagonist, on language function [41]. In this study, four patients with chronic Broca's aphasia were given single doses of propranolol or placebo and had language assessed via performance on the Boston Naming Test (BNT) across three separate drug trials. The authors found consistent small increases in naming performance (average BNT score before drug, 26.3; after drug, 29.0). The authors speculate that the benefits of β-antagonism may be related to suppression of background activity.

Dopamine agonists and L-dopa

Bragoni et al. [42] studied the effects of high-dose bromocriptine (up to 30 mg three times daily) on patients with chronic nonfluent aphasia in a single-cohort study. They found that bromocriptine plus 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 Seniów et al. [43] used a parallel design of 39 patients with subacute stroke randomly assigned to receive 100 mg of L-dopa or placebo. Drug therapy was timed to precede SLT, five times a week, by 30 minutes and continued for 3 weeks. The Boston Diagnostic Aphasia Examination was used as the primary outcome measure. The investigators found improvement on all metrics, but it reached statistical significance only 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. [44] examined the impact of bromocriptine started during the acute phase and continued for 4 months and found no benefit from 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 [45,46].

It is notable that the two studies demonstrating efficacy for dopamine therapy explicitly coupled dopamine therapy with SLT, whereas the three studies that did not show efficacy had no requirement for SLT. This is consistent with the animal literature described previously. These data also are consistent with much of the data from the motor recovery literature, in which L-dopa coupled with physical therapy improved motor outcomes [47,48]. 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 to treat aphasia. Inhibitors of acetylcholinesterase are in widespread use for Alzheimer's disease and generally are safe and well tolerated. In a randomized controlled trial, Berthier et al. [49•] found that patients with chronic aphasia who received 16 weeks of donepezil improved significantly on the Western Aphasia Battery (WAB), 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 central nervous system activity. It facilitates cholinergic and excitatory amine neurotransmission, increases regional cerebral blood flow, and alters neuronal membrane properties [50]. 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 United States and is approved in Europe for treating myoclonus.

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 [51]. A later double-blind placebo-controlled study in chronic aphasia showed improvement on a single subtest of the Aachen Aphasia Test (written language) [52]. Integrating functional neurologic measures into a treatment trial, another study showed increased 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 [53].

Memantine

Memantine is a noncompetitive *N*-methyl-D-aspartate receptor antagonist approved for the treatment of moderate to severe Alzheimer's disease. A single trial examined the efficacy of memantine in treating chronic aphasia due to stroke. Berthier et al. [54] found that 20 mg/d of memantine for 16 weeks, in the absence of SLT, produced enhanced performance on the WAB. Incorporation of constraint-induced aphasia therapy (CIAT; a form of therapy that involves controlled restriction of the use of nonverbal channels of communiction [54]) 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's ($P = 0.041$). This study suggests 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 WAB scores at the onset of CIAT. Given the good efficacy and tolerability profile of combination use of donepezil and memantine for Alzheimer's disease and 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 [56] as well as multiple cognitive domains. Tsikunov and Belokoskova [57] examined the effects of intranasal desmopressin (a V1b and V2 receptor agonist) administration in patients with chronic stroke-related aphasia and observed "good" responses (improvements on at least 3 of 10 language tests) in 13 of 26 subjects. SLT was not incorporated into this trial. One intriguing factor here is the literature supporting V1 agonism and social behavior [56]. It would be interesting to determine whether the language benefits of desmopressin are driven by alterations in social behavior.

Other Biological Interventions

Transcranial magnetic and direct current stimulation

Transcranial magnetic stimulation (TMS) and direct current electrical stimulation (tDCS) are noninvasive brain

stimulation techniques that modulate cortical excitability. There is increasing evidence that these techniques may enhance the effect of training on performance of certain motor tasks as well as some other cognitive tasks, such as aphasia [58••]. 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. [59] to acutely improve the naming ability of Alzheimer's disease patients via stimulation of the dorsolateral prefrontal cortex. 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. [60] used slow repetitive TMS to inhibit the anterior portion of the right-sided homologue of Broca's area in aphasic patients. They reported long-lasting improvements in naming in four patients with Broca-type aphasia in an open-label study. Stimulation approaches also may be incorporated into behavioral paradigms. Floel et al. [61] used tDCS over the left perisylvian 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. Finally, stimulation approaches may enhance traditional therapeutic approaches post-stroke. Hesse et al. [62] combined tDCS with robot-assisted arm training in patients with motor deficits in an uncontrolled pilot study. Interestingly, they found that four of the five aphasic patients in their sample improved on the Aachen Aphasia Test. Clearly, brain stimulation approaches are in their earliest stages, and the aforementioned studies are small and preliminary. However, the relative ease of implementing 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 using cell-based or growth factor–based therapy for stroke, and none of these studies looked at aphasic patients. Based on registration on clinicaltrials.gov, there currently are at least five active trials involving the intravenous infusion of several types of autologous sources of stem cells for acute ischemic stroke, at least five examining the effects of erythropoietin, and at least two examining the effects of G-CSF analogues 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 is 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 predict efficacy in 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 might have enormous benefit, is to withhold interventions that might have negative effects on these processes. Drugs that can adversely affect aphasia recovery include agents used to treat several highly prevalent diseases, particularly in aphasic patients, namely hypertension, coronary artery disease, seizures, anxiety, psychotic symptoms, and gastrointestinal disturbances. Drugs with probable deleterious effects on aphasia are listed in Table 2. General classes of drugs that are most notable in this regard are α-adrenergic antagonists, γ-aminobutyric acid (GABA) potentiators, drugs with anticholinergic side effects, and antiseizure medications, particularly topiramate (most common offender), phenytoin, phenobarbital, and vigabatrin [63–65].

Avoiding potentially deleterious drugs is highly relevant to aphasia rehabilitation as it is currently practiced, independent of the explicit biological interventions discussed here. 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. Thus it is 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.

Treatment of depression

Post-stroke depression is highly prevalent, with estimates ranging from 30% to 60% [66,67], and is highly underdiagnosed [68]. Most common is minor depression, including depressed mood or loss of interest or pleasure, with fewer than five symptoms of major depression [69]. Depression may be particularly difficult to detect in aphasic subjects because of their difficulty in expressing emotions and the possible misattribution of social withdrawal to only language deficits. Aphasic patients, if anything, are more prone to post-stroke depression than their nonaphasic counterparts [70], and may have a greater compromise in their quality of life [71].

Depression may adversely affect language recovery; consequently, depression treatment represents a biological intervention for aphasia that can be used presently. The best data suggest a beneficial role for the tricyclic nortriptyline [72], the highly selective serotonin reuptake inhibitor citalopram [73,74], and more recently, the noradrenergic reuptake inhibitor reboxetine [74]. Recently, we showed that escitalopram treatment helped prevent post-stroke depression, but not more than a behavioral intervention [75].

Table 2. Drugs with potentially deleterious effects on aphasia recovery

Specific drug or agent class	Reason for administration	Neurotransmitter system
Benzodiazepines (eg, diazepam, chlordiazepoxide, lorazepam)	Anxiety	GABA agonist
Clonidine	Hypertension	α_2-adrenergic agonist
Labetalol (predominantly a β-blocker but also an α_1-antagonist)	Hypertension, coronary artery disease	Partial α_1-adrenergic antagonist
Phenoxybenzamine, prazosin	Hypertension	α_1-adrenergic antagonist
Butyrophenones (eg, haloperidol), phenothiazines (eg, chlorpromazine), and related agents (eg, quetiapine)	Psychosis	D_2 dopaminergic antagonist
Butyrophenones (eg, droperidol) and phenothiazines (eg, metaclopramide)	Gastrointestinal disturbances	D_2 dopaminergic antagonist
Barbiturates (eg, phenobarbital)	Seizures	GABA agonist
Phenytoin	Seizures	Not transmitter specific
Topiramate	Seizures, migraine	Glutamate, GABA, possibly others

GABA—γ-aminobutyric acid.

Conclusions

There are increasingly reliable data suggesting a potential beneficial effect potentiation of catecholaminergic, particularly dopaminergic, transmission on aphasia rehabilitation. The data also are promising for drugs that potentiate ACh, as well as for compounds for which 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 using language metrics as primary outcome measures. The nonaphasic 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 multidrug therapy to attack different pathophysiologic pathways, there have been no randomized trials of combination therapy for aphasic stroke therapy. In addition, different etiologic forms of aphasia probably have different natural histories and therefore different sensitivities to pharmacotherapy, and this has not yet been explored. Larger multicenter studies of these questions are needed.

In most cases, drug efficacy has been seen only when coupled with active behavioral interventions, which was strongly predicted by the animal literature. Indeed, such behavioral intervention likely is the engine that drives pharmacologic responses [76••]. Therefore, neither pharmacotherapy nor stimulation methods should be used as a substitute for SLT. In addition, it is likely that different forms of drug therapy will interact optimally with different forms of behavioral interventions, and this should be explored.

It is very likely that pharmacotherapy and stimulation devices will ultimately play a valuable role as adjuncts 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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Disclosure

Dr. Llano is employed by and holds shares in Abbott Laboratories. No other conflicts of interest relevant to this article were reported.

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To our knowledge, this is the only study to induce recovery and track the mechanism of that recovery in an animal cognitive model. The latter point is important because it provides a benchmark with which to evaluate the therapy in clinical trials. If one cannot show via sensitive tools (such as functional MRI) 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.

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This review describes the rationale behind the coupling of physical therapy (particularly constraint-induced movement therapy) with drug or electrical stimulation therapy. The authors describe their own group's experiences with this approach and 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.