NEUROBIOLOGY OF LANGUAGE

Edited by

GREGORY HICKOK
Department of Cognitive Sciences, University of California, Irvine, CA, USA

STEVEN L. SMALL
Department of Neurology, University of California, Irvine, CA, USA

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SECTION P

LANGUAGE TREATMENT

CHAPTER

85

Pharmacotherapy for Aphasia

Daniel A. Llano[1] *and Steven L. Small*[2]

[1]Department of Molecular and Integrative Physiology, University of Illinois at Urbana-Champaign, Champaign, IL, USA; [2]Department of Neurology, University of California at Irvine, Irvine, CA, USA

85.1 INTRODUCTION

Aphasia is one of the most common consequences of stroke, and it is also one of the most feared. Approximately 10–30% of stroke victims suffer from a language deficit after stroke (Bersano, Burgio, Gattinoni, Candelise, & P.S.G., 2009; Pedersen, Stig Jørgensen, Nakayama, Raaschou, & Olsen, 1995; Wade, Hewer, David, & Enderby, 1986), and recovery from a stroke-related language deficit is highly variable and dependent on a range of factors. For example, lesion-related variables, such as the size and location of the stroke, and patient-related variables, such as the patient's age and history of strokes, are likely major determinants in recovery from stroke (Caplan, Hildebrandt, & Makris, 1996; Heiss & Thiel, 2006; Kertesz, Harlock, & Coates, 1979; Lazar & Antoniello, 2008) and are essentially unmodifiable in the postacute setting. Other aspects important in the long-term language recovery of patients, such as prevention of future strokes, design and implementation of a language therapy plan, and pharmacologic therapy, can all be points of successful intervention by the clinician.

In this chapter, we review the literature on pharmacologic approaches to aphasia recovery. Specifically, we attempt to integrate a body of literature on motor stroke recovery in animal models with clinical data examining the effects of drug interventions on aphasia recovery. Herein, we argue that a primary focus for the rehabilitation of patients with aphasia should be pharmacological enhancement of reorganization of neural circuits rather than simply the development of compensatory strategies. As such, we adopt a medical model to the treatment of stroke whereby the therapeutic aim is to guide plasticity with behavioral therapy and to facilitate this plasticity with pharmacological intervention.

85.2 MAJOR CHALLENGES

It is worth noting early in this chapter that there are two significant challenges to making progress in the area of aphasia recovery: limited clinical trial data and lack of animal models for language. Compared with other neurological diseases for which the underlying disease processes may be more homogeneous across subjects and the outcome measures have been validated to be sensitive to pharmacologic intervention, aphasia recovery is in a somewhat disadvantageous position. Strokes are highly variable in location, size, and even etiology. In addition, the term "aphasia" is quite broad and can include difficulties ranging from dysfluency to patients who are highly (or overly) fluent but with difficulties in the understanding and formulation of language. Such heterogeneity in language deficits likely reflects heterogeneity in lesion location, size, and etiology. The latter point is important because the term "stroke" may encompass a range of underlying pathophysiological mechanisms, such as large-vessel atherosclerotic disease, cardioembolic disease, small vessel disease, venous thrombosis, and intracranial hemorrhage. It is likely that stroke-related deficits caused by different underlying pathophysiologic mechanisms will have different time courses of recovery and different sensitivities to pharmacological therapy. Similarly, although there are many different rating scales available to evaluate the severity of aphasia (Shewan & Kertesz, 1980; Strauss, 2006), the underlying heterogeneity in aphasia types and etiologies and the lack of validation of such scales for sensitivity to drug manipulations create challenges for the use of a single instrument to evaluate the efficacy of drug therapies for aphasia. These factors have contributed to the relatively small number of clinical trials performed to examine the

potential for drugs to treat aphasia. For example, a recent (July 2013) search on www.clinicaltrials.gov revealed four studies actively recruiting subjects for drug interventions for aphasia. When evaluating the clinical literature on aphasia drug therapies, these challenges make it difficult to apply the same criteria as those for diseases that are more amenable to study using standard clinical trial approaches.

Another factor affecting progress in this area is the lack of adequate animal models. Animal models serve as a proving ground for putative new therapies and have been shown to be indispensable for the development of drug therapies for epilepsy, multiple sclerosis, and Parkinson disease (Dauer & Przedborski, 2003; Gold, Linington, & Lassmann, 2006; McNamara, 1985), and have led to great insights to the underlying pathophysiology of other diseases such as Alzheimer disease (Price & Sisodia, 1998). Currently, however, there are no established animal models for language—at least language as humans experience it. Although this is a topic that has been hotly debated in the literature (Hauser, Chomsky, & Fitch, 2002), and although the details of this are well beyond the scope of this chapter, it is safe to say that there are no established models with a high enough throughput to allow the vetting of potential drug therapies. Instead, the field has relied on animal models of motor stroke. Here, the literature is quite mature, many approaches to inducing stroke exist (middle cerebral artery ligation, photothrombosis, etc.) (Carmichael, 2005), and the outcome measures of motor recovery are highly quantifiable. Therefore, for the current discussion we assume that at least some of the mechanisms of repair and reorganization of neural structures involved in recovery from motor stroke are similar to those involved with language recovery, although more work is greatly needed in this area to validate this assumption.

Despite the challenges described, it is worth noting that now, more than ever, we are strategically positioned for great advances in the development of drug therapy for aphasia. Human and animal imaging technologies have advanced to the point that the impact of drug and/or behavioral therapy on neural networks can be studied in humans and animals using very similar imaging technologies, facilitating comparisons of the pharmacodynamics of putative therapies across species (Bifone, Gozzi, & Schwarz, 2010; Rumple et al., 2013). Therefore, the impact of drug and behavioral interventions, both on task-related activation patterns and resting states, as well as structural imaging of gray and white matter (Jang, 2011; Schwarz et al., 2011) can be assessed and compared. It is hoped that this chapter will serve as a starting point to initiate future mechanistic studies in this area.

85.3 MECHANISMS OF RECOVERY AND PHARMACOTHERAPY

There is a substantial body of work documenting the natural history and the impact of pharmacological modulation of stroke recovery in animal models. Most of this research has involved lesions of the motor cortex and has used motor output as its focus for efficacy. Once a small area of cortex is lost, a host of short-range and long-range mechanisms are engaged to facilitate reorganization of cortical function (Hermann & Chopp, 2012; Murphy & Corbett, 2009). These mechanisms are activity-dependent and include axonal sprouting (Dancause et al., 2005; Overman et al., 2012), which can extend distances >1 cm across the adult primate cortex, elaboration of dendritic spines (Brown & Murphy, 2008; Ueno et al., 2012), migration of subventricular stem cells to the infarction zone (Danilov, Kokaia, & Lindvall, 2012; Kahle & Bix, 2013; Lichtenwalner & Parent, 2005), and modulation of the strength or excitability of existing synapses (Di Filippo et al., 2008; Jaenisch, Witte, & Frahm, 2010; Yao et al., 2005). Because such mechanisms are likely to be differentially sensitive to pharmacological manipulation, one might postulate that different etiological mechanisms of infarction would require different forms of intervention. It is also possible that some forms of modulation of synaptic strength may be maladaptive (Costigan, Scholz, & Woolf, 2009; Di Filippo et al., 2008) and therapeutic modalities, appropriately targeted and timed, may be used to interfere with such forms of pathological plasticity.

Several concepts have arisen from the animal literature on stroke recovery (and lesion recovery more generally) that may inform our review of the literature on drug therapy for aphasia. First, it is clear that maximal benefit is derived not from drugs or rehabilitation approaches on their own, but with *combination* therapy. There are many studies supporting the idea that synaptic plasticity, which is presumed to be the dominant mechanism underlying synaptic rewiring responsible for stroke recovery, is greatly facilitated when neurotransmitter manipulations are accompanied by behavioral training (Bao, Chan, & Merzenich, 2001; Kilgard & Merzenich, 1998; Schultz, 2002). Further, many of the classes of drugs discussed within this review have been explicitly modeled to help support and strengthen neural networks being modified by behavioral training (Korchounov & Ziemann, 2011), such that their efficacy in the absence of behavioral training may be greatly reduced. Taken further, one might even speculate that drugs that support synaptic plasticity, when used in the absence of targeted behavioral therapy, may actually reinforce maladaptive

patterns of neuronal activity. In addition, it is of high clinical relevance that the cerebral cortex undergoes plastic changes for at least *months* after stroke, and that these adaptive changes occur not only in the tissue immediately surrounding the lesion but also in areas remote from the site of injury (Jenkins & Merzenich, 1987; Nudo & Friel, 1999; Nudo, Wise, SiFuentes, & Milliken, 1996; Xerri, Merzenich, Peterson, & Jenkins, 1998). Finally, the animal studies suggest that certain classes of drugs commonly used in clinical practice, particularly sedating drugs such as benzodiazepines, can *diminish* the reorganization of brain networks after injury (Goldstein, 2000; Larson & Zollman, 2010). Given the emerging recognition of poststroke depression and anxiety (Aben et al., 2003; Barker-Collo, 2007) and the relatively high incidence of seizures after stroke (Lossius, Rønning, Mowinckel, & Gjerstad, 2002; Olsen, 2001), both of which may be treated with benzodiazepines, these data indicate that nonsedating alternatives may be more appropriate to avoid interference with poststroke recovery mechanisms.

85.3.1 Animal Studies: Catecholamine-Based Therapy

There is a rich history of the use of catecholamine augmentation as adjunctive therapy to enhance stroke recovery. Catecholamines are a natural target for stroke therapeutics because it has long been known that there are significant alterations in brainstem and cortical catecholamine levels in the acute and subacute periods after stroke (Brown, Carlson, Ljunggren, Siesjö, & Snider, 1974; Cohen, Waltz, & Jacobson, 1975; Robinson, Shoemaker, & Schlumpf, 1980; Robinson, Shoemaker, Schlumpf, Valk, & Bloom, 1975). In addition, lesions to the noradrenergic afferents from the locus ceruleus have been shown to impair recovery of animals with contralateral sensory-motor cortical injuries (Goldstein & Bullman, 1997), and pharmacological antagonism of alpha adrenergic receptors with phenoxybenzamine delays spontaneous recovery from cortical damage (Feeney & Westerberg, 1990).

A number of neurophysiological mechanisms are postulated to underlie the beneficial effects of catecholamine enhancement of stroke recovery. Norepinephrine and dopamine modulate multiple forms of synaptic plasticity, including long-term potentiation and long-term depression, and spike timing-dependent plasticity (Carey & Regehr, 2009; Clem & Huganir, 2013; Dommett, Henderson, Westwell, & Greenfield, 2008; Edelmann & Lessmann, 2013; Ghanbarian & Motamedi, 2013; Gu, 2002; Wolf, Mangiavacchi, & Sun, 2003). These data would suggest that the impact of catecholamine modulation on recovering neural circuits would be highly activity-dependent, which is consistent with the data presented. Other studies have shown that catecholamines may enhance neural regeneration (Hiramoto, Ihara, & Watanabe, 2006; Lloyd, Balest, Corotto, & Smeyne, 2010; Spiegel et al., 2007) or axonal sprouting (Papadopoulos et al., 2009). Overall, these data suggest that catecholamine augmentation may function to alter neuronal plasticity on several different temporal and spatial scales.

The paradigm for the study of catecholamine-based therapy was established by early work demonstrating that administration of a single dose of dextroamphetamine (D-amphetamine, which causes the release of stored norepinephrine, dopamine, and, to a lesser degree, serotonin) can facilitate recovery of beam-walking behavior after lesion of motor cortex (Feeney, Gonzalez, & Law, 1982). Importantly, drug effects on recovery were only seen when drug administration was coupled with the promotion of physical activity. This basic finding of the dependency between active training and catecholamine augmentation for maximum motor recovery has been reproduced in animals several times in several stroke models (Barbay et al., 2006; Beltran, Papadopoulos, Tsai, Kartje, & Wolf, 2010; Papadopoulos et al., 2009; Ramic et al., 2006; Rasmussen, Overgaard, Hildebrandt-Eriksen, & Boysen, 2006). For example, in the visual system, bilateral visual cortex lesions in cats leading to deficits in depth perception can be ameliorated with a combination of visual experience and dextroamphetamine administration (Feeney & Hovda, 1985). No benefit was seen when either the drug or behavioral training were given independently of each other.

The receptor pharmacology of the beneficial effects D-amphetamine is not yet entirely clear. The effect of D-amphetamine on motor recovery can be blocked by the haloperidol (Feeney et al., 1982), a D2 antagonist, which also has weaker antagonism at the alpha1 adrenoreceptor. In addition, as described, alpha1 receptor blockade impaired spontaneous recovery (Feeney & Westerberg, 1990) and treatment with intraventricular norepinephrine, but not dopamine, and reproduced the beneficial effect of D-amphetamine (Boyeson & Feeney, 1984). Further, findings in animals that have recovered from brain trauma that show that alpha adrenergic antagonists, such as phenoxybenzamine, can cause the recrudescence of lesion-related deficits long after functional recovery has occurred (Feeney, De Smet, & Rai, 2004) and suggest that a long-standing and tonic increase in norepinephrine is needed to restore function in certain neural networks. Most recently, motor recovery in a rat stroke model

was facilitated by atipamezole and alpha-2 blocker, which elevates synaptic norepinephrine levels, with little effect on dopamine (Beltran et al., 2010; Gobert, Billiras, Cistarelli, & Millan, 2004). These data suggest that norepinephrine, acting on alpha adrenergic receptors, is the primary driver of functional recovery in these models. However, it has been suggested, primarily based on data from levodopa-enhanced word-list learning in normal humans and the low rates of conversion of levodopa to norepinephrine (~5%), that dopamine may also play a significant role (Breitenstein et al., 2006). The mixed clinical picture surrounding drugs like amphetamine and levodopa, which activate multiple receptor types, suggests that there is a need to more precisely define the mechanism of action of these drugs to target the efficacious mechanisms.

85.3.2 Animal Studies: Cholinergic Mechanisms

Luria postulated that enhancement of acetylcholine levels via the natural cholinesterase inhibitor galanthamine (precursor to modern Alzheimer's drug, galantamine), may promote functional language recovery after stroke (Luria, Naydyn, Tsvetkova, & Vinarskaya, 1969). In general, these agents have been particularly relevant to the treatment of Alzheimer disease, for which there is a cholinergic model that relates atrophy in the nucleus basalis of Meynert (the source of all cerebral cortical acetylcholine) to the pathophysiology of Alzheimer disease (Whitehouse, Price, Clark, Coyle, & DeLong, 1981). Acetylcholine is thought to be involved in a number of aspects of cognition, including sensory perception, selective attention, associative learning, and memory, as well as experience-dependent plasticity (Baskerville, Schweitzer, & Herron, 1997; Yu & Dayan, 2002). Very suggestive evidence for the potential for acetylcholine augmentation to be used as a therapeutic modality to enhance plasticity is derived from findings in the auditory cortex, where experience-dependent alterations of sensory maps were greatly enhanced when sensory stimulation was coupled with stimulation of cholinergic fibers from the basal forebrain (Kilgard & Merzenich, 1998). Notably, map reorganization parameters were directly related to the specific training stimuli used, emphasizing the importance of understanding the interactions between specific speech and language therapies with pharmacologic intervention. One view is that cholinergic neurons from the basal forebrain serve a modulatory function by *marking* behaviorally salient stimuli (Kilgard & Merzenich, 1998). This experience-dependent and acetylcholine-dependent map reorganization learning is probably mediated by muscarinic cholinergic receptors, rather than nicotinic receptors, because this learning can be blocked by scopolamine, a muscarinic antagonist (Thiel, Friston, & Dolan, 2002).

Despite the well-recognized role for acetylcholine in activity-dependent plasticity, there are comparatively little data supporting enhancement of cholinergic activity for motor stroke recovery in animal models. A study using galantamine in a motor stroke model did not show efficacy (Zhao, Puurunen, Schallert, Sivenius, & Jolkkonen, 2005), whereas the data for nicotine administration are mixed (Gonzalez, Gharbawie, & Kolb, 2006; Lim, Alaverdashvili, & Whishaw, 2009). It is interesting to note that the muscarinic blocker scopolamine has been shown to have some *beneficial* effects in early recovery in animal models of traumatic injury (Lyeth et al., 1992), possibly by reducing cholinergic neuronal activation (Saija et al., 1988), but the window for such an advantage is very short (15 min) (Hamm, O'Dell, Pike, & Lyeth, 1993). This is similar to what has been seen with several "neuroprotective" agents, such as NMDA(N-methyl-D-aspartate)-receptor antagonists (Villmann & Becker, 2007) and gamma-amino butyric acid (GABA)-potentiators (Green, Hainsworth, & Jackson, 2000), reinforcing the idea that the *timing* of intervention will play a critical role in the development of aphasia treatment strategies.

85.3.3 Animal Studies: Serotonin and Brain-Derived Neurotrophic Factor

Serotonin regulates some forms of cortical map reorganization (Gu & Singer, 1995; Jitsuki et al., 2011; Vetencourt, Tiraboschi, Spolidoro, Castrén, & Maffei, 2011) and adult neurogenesis in the hippocampus (Daszuta, 2011; Li et al., 2009), although the evidence supporting a role for serotonin in promoting neural reorganization in the chronic stroke setting is relatively sparse. More attention has been given to the ability of serotonin to enhance the expression of the ubiquitously expressed Brain-Derived Neurotrophic Factor (BDNF). Rodent studies have shown that BDNF increases both locally and remotely after the induction of stroke (Béjot et al., 2011), and that inhibition of BDNF using antisense oligonucleotides impair stroke functional recovery from motor cortex stroke (Ploughman et al., 2009). This study also revealed a synergistic interaction between physical therapy and BDNF expression. Other rodent work has demonstrated that exogenous BDNF administration facilitates motor recovery from acute stroke (Schabitz et al., 2007). Despite the suggestive findings regarding BDNF and stroke, there are major hurdles to the translation

of this therapy to the clinic. Delivery of such a large molecule to the central nervous system (CNS) poses a problem, particularly in the chronic phase of stroke when the blood–brain barrier has reconstituted. This provides an opportunity to drive BDNF expression indirectly via serotonin augmentation (e.g., through the use of selective serotonin reuptake inhibitors [SSRIs]). It is not clear, however, whether serotonin augmentation through SSRIs is sufficient to drive BDNF expression to sufficient levels to promote recovery because SSRI studies in chronic stroke have had a mixed track record (Boyeson, Harmon, & Jones, 1994; Windle & Corbett, 2005). It may be that extrasynaptic serotonin is necessary to promote BDNF expression, or that only specific serotonin receptor subtypes are responsible for BDNF expression (there are at least seven subtypes of the serotonin receptor) and should be targeted more specifically. There is another unanswered question regarding the ability of BDNF to promote recovery in the chronic phase of stroke. BDNF has neuronal protectant properties (Marini et al., 2004), and most studies to date have been performed in the acute phase.

85.3.4 Animal Studies: GABAergic Mechanisms

Another agent that has received attention in animal studies is GABA. GABA is particularly interesting because its action on neurons is primarily inhibitory (Hendry, Schwark, Jones, & Yan, 1987). Augmentation of GABAergic neurotransmission, either via benzodiazepines or via barbiturates, has been a popular drug development strategy to promote neuronal protection during the acute phase of stroke, presumably by limiting neuronal metabolic demand during periods of high metabolic stress (Green et al., 2000). In the chronic phase, there is little evidence that GABA potentiation promotes reorganization after stroke. For example, intracortical infusion of GABA exacerbates the hemiparesis produced by a small motor cortex lesion in rats (Schallert et al., 1992). In addition, the short-term administration of diazepam (a benzodiazepine and indirect GABA agonist) permanently impedes sensory cortical recovery from neocortical injury (Schallert, Hernandez, & Barth, 1986). Furthermore, the GABA potentiator phenobarbital also interferes with recovery from brain injury (Hernandez & Holling, 1994; Montanez, Kline, Gasser, & Hernandez, 2000). Another approach involves removal of GABAergic inhibition, which may promote cortical map reorganization, for which there is some evidence (Jacobs & Donoghue, 1991). However, such an approach would pose a challenging translational strategy because blockade of GABA significantly lowers seizure threshold (Seger, 2004) and chronic stroke patients have a risk of seizure that is higher than baseline (Asconapé, 1991; Lossius et al., 2002; Olsen, 2001).

85.3.5 Animal Studies: Extracellular Matrix-Based Mechanisms

Stroke induces the expression of a number of extracellular molecules that are potentially hostile to axonal outgrowth. These include myelin-associated extracellular molecules, such as Nogo-A, myelin-associated glycoprotein, and oligodendrocyte-myelin glycoprotein, and extracellular matrix proteins, such as tenascin and chondroitin sulfate proteoglycans (Carmichael, 2006). Among these, the Nogo-A system has been well-characterized, and inhibitors of this system have moved forward into clinical trials of spinal cord injury and are under consideration for stroke. In animal models of subacute motor cortical stroke, inhibition of Nogo-A activity via passive immunization resulted in enhanced recovery of motor function in several studies (Brenneman et al., 2008; Papadopoulos et al., 2009; Tsai et al., 2007). Of potential relevance for the therapy of aphasia are the findings that intraventricular administration of anti-Nogo antibodies promoted recovery in a rodent model of hemispatial neglect (Brenneman et al., 2008) and poststroke spatial memory deficit (Gillani et al., 2010), suggesting that Nogo inhibition may ameliorate cognitive dysfunction. No studies of anti-Nogo therapy, to our knowledge, have been performed during the late chronic phase of stroke. However, because the studies referenced have not demonstrated any alteration in infarct size after anti-Nogo therapy, anti-Nogo therapy may promote neural reorganization rather than neuronal protection. This supposition suggests that anti-Nogo therapy represents at least a feasible path forward for studies of chronic stroke patients.

One potential concern with the body of rat literature documenting the benefits of anti-Nogo therapy is that in both the motor stroke studies (Papadopoulos et al., 2009; Tsai et al., 2007) and at least one of the "cognitive" stroke studies (Brenneman et al., 2008), recovery was in large part mediated by activation of contralesional structures. This suggests that anti-Nogo therapy may promote sprouting of long-range axons of contralesional origin rather than remaining ipsilateral axons. Because recovery in human motor stroke (Fridman et al., 2004), aphasia (Heiss et al., 1997; Karbe et al., 1998; Szaflarski, Allendorfer, Banks, Vannest, & Holland, 2013), and neglect (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005) is likely optimally mediated by ipsilesional structures, promotion of sprouting of contralesional axons may not be an optimal recovery

strategy. It is not known if the preference for the contralesional structures is specific to anti-Nogo therapy or to rodent stroke recovery in general.

85.3.6 Animal Studies: Combining Drug and Behavioral Therapy

A feature common to most pharmacotherapy for chronic stroke is the requirement that physical therapy must be used to materialize the benefits of drug administration. By extension, speech and language therapy (SLT) may have a similar role in the pharmacotherapy for aphasia. Because certain forms of neuronal plasticity can be maladaptive (Costigan et al., 2009; Di Filippo et al., 2008), it is crucial that alterations of synaptic strength or number are not haphazard. In addition, because most drugs uniformly bathe the brain without the ability to specifically modify damaged circuitry, SLT is necessary to target particular areas for synaptic modification. As such, drug therapy likely plays a permissive role in stroke recovery. There may be exceptions to this. For example, stem cell therapy may be able to target specific areas of the brain that overexpress molecular factors in damaged areas (see Chapter 86 on cell-based therapies). It is unknown whether these molecular targets are sufficiently specific to allow neural repair without the guidance of behavioral training. It will be important to clarify this issue in animal models because it has therapeutic implications. For example, for patients unable to participate in rehabilitation, it may very well be counterproductive to offer permissive drug therapy, such as catecholamine augmentation, because these drugs may reinforce inappropriate circuitry. However, such patients may be candidates for therapies that can target damaged circuitry, such as stem cell therapy. Continued exploration of the combination of drug therapy and physical therapy in animal models will assist in guiding these decisions.

85.4 HUMAN STUDIES: PHARMACOTHERAPY FOR APHASIA

There is a long history of attempts at aphasia pharmacotherapy (Bergman & Green, 1951; Linn, 1947; Sarno, Sarno, & Diller, 1972; West & Stockel, 1965) (for a review of these studies, see Small, 1994 or Small, 2001). The outcomes of these studies were generally negative, likely related to inadequate scientific rationales or poor study design (e.g., underpowered studies, poor dose selection, inappropriate outcome measures). The animal data would suggest that the most promising targets for pharmacotherapy for aphasia would be accentuation of norepinephrine and dopamine levels coupled with behavioral therapy. Fortunately, this hypothesis lends itself to direct clinical translation because of the existence of several approved drugs that increase brain catecholamine levels (D-amphetamine, levodopa, etc.). Regarding study design, in general, 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 due to plastic changes in the brain. Unfortunately, very few studies have had this type of design. In addition, much of the literature utilizes heterogeneous outcome measures and many studies provide few details regarding the results, making meta-analyses very challenging. This section reviews the existing literature on drug therapy of aphasia. To our knowledge, there have been a total of 18 prospective, double-blind studies involving patients with subchronic or chronic stroke that used a language metric as a primary outcome measure, and we review these studies here. The attention here is restricted to small-molecule therapy in the subacute and chronic phases of aphasia due to stroke.

85.4.1 Human Studies: Noradrenergic Agents

The animal data tell a compelling story that enhancement of catecholamine levels, coupled with physical therapy, can promote neural reorganization and functional recovery even during the chronic phase of motor stroke. The two most highly studied catecholamines for stroke recovery are dopamine and norepinephrine. Dopamine and norepinephrine poorly cross the blood–brain barrier and are therefore rarely administered in these studies. Instead, other drugs such as D-amphetamine, which indirectly elevates synaptic catecholamine levels, or related compounds are administered. Other approaches have been to block the reuptake of norepinephrine and dopamine with methylphenidate. None of these drugs permit the isolation of noradrenergic from dopaminergic effects, although it has been argued that dopamine may play a dominant role in language recovery.

We are aware of four prospective, placebo-controlled, double-blind studies that examine the effects of D-amphetamine on language function in aphasic patients. The largest and most frequently cited study is that by Walker-Batson et al. (2001). In this study, subjects with subacute stroke were treated with D-amphetamine or placebo, and treatment was coupled with traditional speech therapy over a 5-week period.

A greater percentage of active subjects demonstrated improvement on the Porch Index of Communicative Ability (PICA) scale at the 6-week time point than their counterparts who received placebo (83% vs. 22%); improvement was assessed 1 week after the last dose of drug. There was a nonsignificant trend for a persistent benefit at 6 months after dosing. This study was confounded by differences in age (D-amphetamine patients were 9.5 years younger) and amount of therapy received (D-amphetamine patients received 21% more therapy time). The authors found that significant differences were maintained after adjusting for baseline age; unfortunately, there was no adjustment performed for therapy time. A more recent study by Whiting, Chenery, Chalk, and Copland (2007) using a double-blind, placebo-controlled, crossover design in two patients with chronic aphasia from stroke also demonstrated improvements in language function associated with D-amphetamine administration. In this study, naming improved in both patients (but reached statistical significance in only one patient) during periods when they received D-amphetamine plus language therapy compared with periods when they received placebo plus language therapy. This benefit persisted 1 month after cessation of drug and language therapy. Clearly, a crossover study with a behavioral outcome such as this study is potentially compromised by a period effect because of learning by the patient, the investigator, or both, over the course of the trial. These two small studies, each with design inadequacies, are at least suggestive of signals of efficacy for D-amphetamine when coupled with SLT for chronic aphasia.

Two earlier placebo-controlled studies did not show a benefit of D-amphetamine therapy. McNeil et al. (1997) conducted a crossover, multiple-baseline study that examined the effects of D-amphetamine or selegiline, with and without lexical-semantic activation inhibition therapy (L-SAIT), in two patients with chronic aphasia from stroke. Both patients responded well to L-SAIT, but there was not consistent improvement across several language measures when L-SAIT was combined with pharmacotherapy. Darley, Keith, and Sasanuma (1977) examined the effects of 3 days of 20 mg of daily methylphenidate administration on performance on PICA in 14 subchronic or chronic aphasia patients. The trial was a crossover design with no washout period, and no SLT was given. The subjects also underwent 3 days of daily 20-mg chlordiazepoxide administration. The absence of a washout period and the inclusion of traumatic brain injury patients in this study make this study particularly difficult to interpret.

In addition to the data on aphasic subjects, D-amphetamine coupled with SLT has been shown to improve language performance and alter the activation of language-related networks in the brain of healthy nonaphasic subjects. Breitenstein et al. (Breitenstein et al., 2004) taught 40 healthy subjects an artificial vocabulary of 50 words via word–picture matching and coupled this training with D-amphetamine or placebo administration. They found that D-amphetamine enhanced learning of the artificial words in the active group compared with placebo, and that this difference persisted 1 month after drugs, suggesting that enhanced performance was not simply a nonspecific effect of arousal. In a similar study, Whiting, Chenery, Chalk, Darnell, and Copland (2007) found that amphetamines enhanced new word learning in healthy subjects, and that there was no correlation between word learning and attention, mood, or cardiovascular arousal that would suggest a specific effect of D-amphetamine on the trained networks. Supporting the idea that D-amphetamine specifically influences the activity of behaviorally activated networks are two pharmacological MRI studies. Uftring et al. (2001) demonstrated that D-amphetamine specifically increased activation in auditory cortical regions during tone discrimination tasks and enhanced activation of motor cortical areas during motor tasks. Similarly, Sommer et al. (2006) found that D-amphetamine administration during verb generation and semantic decision task (using a conjoint analysis) increased overall left hemispheric activation and increased activation of Broca's areas, the right homolog of Broca's area, and left supramarginal gyrus, but it 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 nonspecifically promoting arousal.

Of importance, and in concordance with the animal model studies (Feeney et al., 1982; Feeney & Hovda, 1985), the studies showing beneficial effects of sympathomimetics (on motor or language) (Crisostomo, Duncan, Propst, Dawson, & Davis, 1988; Grade, Redford, Chrostowski, Toussaint, & Blackwell, 1998; Walker-Batson, Devous, Curtis, Unwin, & Greenlee, 1991; Walker-Batson, Smith, Curtis, Unwin, & Greenlee, 1995) share the common feature of evaluating D-amphetamine as an adjunct to behavioral or physical therapy rather than alone. This is consistent with the view espoused at the outset regarding the role of behavior in modifying neural circuits and the notion that, without training, even extensively reorganized or remodeled neural circuits are not likely to improve performance.

Although not reviewed here in detail, it is worth noting that after early promising trials, D-amphetamine has failed to show improvement in several more recent well-designed, appropriately powered trials of recovery of motor function after stroke in humans

(Gladstone et al., 2006; Platz et al., 2005; Sonde & Lökk, 2007; Sprigg et al., 2007). It is difficult to predict whether D-amphetamine for aphasia would meet a similar fate if tested in larger trials. One factor that differs between motor and language studies, and across language studies, is the type and magnitude of behavioral therapy given to patients. Might some forms of behavioral therapy be more amenable to drug facilitation than others? The constraint-induced movement therapy typically used in modern stroke motor recovery trials may promote plasticity near or around damaged neural networks, whereas other forms of therapy may be more likely to promote reorganization of different compensatory neural networks. Given the paucity of efficacious drug therapy for chronic aphasia, the good safety profile of D-amphetamine and the promising data from Walker-Batson et al. and Whiting et al., larger trials are merited. It may be interesting to independently vary the type of SLT offered to D-amphetamine patients to probe the drug–behavior interactions mentioned.

Although most of the basic and clinical literature has been directed toward the investigation of the benefits of sympathomimetic compounds as described, an additional report has been published documenting the effect of propranolol, a beta1/beta2 adrenergic antagonist, on language function (Beversdorf et al., 2007). In this double-blind crossover study, four chronic Broca's aphasic patients were administered single 40-mg 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 before drug = 26.3, after drug = 29.0). This report is consistent with a previous abstract demonstrating benefit of propranolol on language performance (Porch, Wyckes, & Feeney, 1985). The authors speculate that the benefits of beta antagonism may be related to suppression of background activity (as discussed by Hasselmo, Linster, Patil, Ma, & Cekic, 1997) or, less likely, in their view, to the anxiolytic properties of propranolol.

85.4.2 Human Studies: Dopamine Agonists and Levodopa

Several studies have examined the role of dopamine in aphasia recovery by either providing bromocriptine, a D2 agonist, or levodopa, the precursor to dopamine, with a peripheral decarboxylase inhibitor to prevent peripheral conversion of levodopa to dopamine. These drugs have a long track record with a good safety profile and less abuse liability than D-amphetamine. We have found six prospective, double-blind, placebo-controlled studies of these drugs in chronic aphasia.

Bragoni et al. (2000) studied the effects of high-dose bromocriptine (up to 30 mg three times per day) on 11 chronic nonfluent aphasics. They utilized a single cohort study, and each subject was compared with his/her own baseline. They found that bromocriptine plus SLT for 60 days improved performance on several language metrics over SLT alone. The benefit was sustained after a 60-day washout of the drug for several metrics but was only statistically significant for reading comprehension. As suggested by the Whiting et al. (2007) study of D-amphetamine, a single cohort study such as this is potentially compromised by a period effect. A recent study by Seniów, Litwin, Litwin, Lesniak, and Czlonkowska (2009) utilized a parallel design of 39 patients with subacute stroke randomized to receive either 100 mg levodopa or placebo. Drug therapy was timed to precede five-times-weekly SLT by 30 min and was continued for 3 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. Levodopa patients were younger than placebo subjects by 6.3 years, potentially confounding the analysis, but the investigators found that age was not associated with BDAE outcome.

Several other studies of dopamine-based therapy did not show efficacy. Ashtary, Janghorbani, Chitsaz, Reisi, and Bahrami (2006) examined the impact of bromocriptine, 10 mg daily, started during the acute phase and continued for 4 months; 19 active patients and 19 placebo patients were enrolled. SLT was not required during this study, and it is not clear if any of the subjects received SLT. The investigators did not find any benefit of bromocriptine administration on a standardized Persian language test. Sabe, Salvarezza, García Cuerva, Leiguarda, and Starkstein (1995) reported the results of a crossover study of seven subjects with chronic nonfluent aphasia who received up to 60 mg daily of bromocriptine for 6 weeks. There was no requirement for SLT. The authors found similar performance during both the bromocriptine periods and the placebo periods. Unfortunately, their randomization scheme placed all subjects into the drug arm first, raising the possibility that a practice effect benefited the placebo period. In a similarly designed study, Gupta, Mlcoch, Scolaro, and Moritz (1995) studied the effect of up to 45 mg of bromocriptine over 10 weeks in patients with chronic aphasia. There was no requirement for SLT. This study had a more balanced randomization scheme than that of Sabe et al., and the authors found no influence of bromocriptine over a wide range of language metrics. Most recently, Leemann et al. observed no benefit of 2 weeks of

levodopa plus benserazide versus placebo when coupled with intensive computer therapy in the subacute period after stroke (Leemann, Laganaro, Chetelat-Mabillard, & Schnider, 2011).

It is notable that the two studies that demonstrated efficacy for dopamine therapy explicitly coupled dopamine therapy with SLT, whereas three out of four 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 human motor recovery literature, where levodopa, when coupled with physical therapy, has improved motor outcomes (Rösser et al., 2008; Scheidtmann, Fries, Müller, & Koenig, 2001). As recently noted (Gill & Leff, 2014), a relatively narrow range of dopaminergic agents and doses has been explored in these studies. The totality of the data, although incomplete, suggests that bromocriptine or levodopa therapy, coupled with SLT, may hold promise for aphasia treatment.

85.4.3 Human Studies: Cholinergics and Anticholinergics

Acetylcholine-augmentation as a therapeutic approach is supported by findings that there might be a relative lateralization of cholinergic projections (Bracco, Tiezzi, Ginanneschi, Campanella, & Amaducci, 1984) and that methylscopolamine, an anticholinergic drug, can impair phonological and lexical processing in normal adults (Aarsland, Larsen, Reinvang, & Aasland, 1994). Despite these findings and the body of neurophysiological data on the role of cholinergic projections in modulating neural plasticity and the neuropsychological data documenting its role in learning and memory described, there have been relatively few attempts to modulate this system for the treatment of aphasia. Inhibitors of acetylcholinesterase have widespread use for Alzheimer disease and, in general, have good safety and tolerability profiles. There have been several open-label pilot studies that showed signals of efficacy (Berthier, Hinojosa, Martin Mdel, & Fernandez, 2003; Pashek & Bachman, 2003; Tanaka, Miyazaki, & Albert, 1997; Tsz-Ming & Kaufer, 2001). One single case study involved a patient with a small subcortical lacunar infarction. Dopamine agonist therapy was ineffective, but donepezil led to a significant improvement in fluency (Hughes, Jacobs, & Heilman, 2000).

We are aware of one randomized controlled trial that examined the utility of cholinesterase therapy for stroke-related aphasia. Berthier et al. (2006) studied the effect of 16 weeks of donepezil (up to 10 mg daily) in patients with chronic aphasia. This was a parallel study design with 13 individuals in each group, and all patients received standard SLT. The subjects were well-matched at baseline. The investigators found that the donepezil group 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. There were trends for improvement regarding spoken word−picture matching and spoken sentence−picture matching. 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 with the effects of donepezil on the improvement of patients with Alzheimer disease (Rogers, Farlow, Doody, Mohs, & Friedhoff, 1998). Given these short-term improvements, it would be interesting to determine if the improvements on language tests are related to an overall improvement across multiple domains of cognition, which has been seen with donepezil, or whether they are specific to language. If so, then that would imply that the benefits of donepezil may not be dependent on SLT and therefore may become a therapeutic option for those patients who may not have access to SLT. These data are consistent with a more recent open-label study demonstrating efficacy of another cholinesterase inhibitor, galantamine, relative to control subjects, for the treatment of chronic poststroke aphasia (Hong, Shin, Lim, Lee, & Huh, 2012).

85.4.4 Human Studies: Piracetam

Piracetam is a derivative of GABA and has a range of effects on the CNS. Piracetam facilitates cholinergic and excitatory amine neurotransmission (Giurgea, Greindl, & Preat, 1983; Vernon & Sorkin, 1991), increases regional cerebral blood flow (Jordaan, Oliver, Dormehl, & Hugo, 1996), and alters neuronal membrane properties (Müller, Eckert, & Eckert, 1999). It has been claimed that this agent improves learning and memory, but it is not clear which of its biological effects (e.g., neuroprotective, circulatory, or others) are responsible for the purported cognitive benefit (Malykh & Sadaie, 2010). Piracetam is currently available as a nutritional supplement in the United States and is approved for the treatment of myoclonus in Europe.

The data on piracetam for aphasia are mixed. One large multicenter trial (n = 927) aimed to treat all stroke patients within 12 h and used a variety of outcome measures, including assessment of aphasia. This study showed no effect on the primary outcome measure of neurological status (Barthel Index and

Orgogozo scale) at 4 weeks (De Deyn, Reuck, Deberdt, Vlietinck, & Orgogozo, 1997). A post hoc analysis of an "early treatment subgroup" (defined prospectively as within 6 h, but retrospectively as within 7 h) showed some benefit of piracetam. This was particularly true in the moderate to severe subgroup (De Deyn et al., 1997; Orgogozo, 1999). Of these patients, approximately one-third (n = 373) were aphasic, and aphasia recovery at 12 weeks was better in the piracetam group than in the control group, particularly for the early treatment subgroup (Huber, 1999; Orgogozo, 1999).

In postacute and chronic aphasia, several randomized controlled trials have been performed. Enderby et al. observed significant improvements 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 (Enderby, Broeckx, Hospers, Schildermans, & Deberdt, 1994). A later double-blind, placebo-controlled study involving chronic aphasia showed trends for improvements across all subsets of the Aachen Aphasia Test, which only reached statistical significance written language (Huber, Willmes, Poeck, Van Vleymen, & Deberdt, 1997). Integrating functional imaging measures into a treatment trial, another study showed an increase in task-related blood flow in several left hemisphere regions generally associated with language over the course of the treatment period; more increase in blood flow in the treatment group than the placebo group. The piracetam group improved on six language measures and the placebo group improved on three (Kessler, Thiel, Karbe, & Heiss, 2000). Most recently, Güngör, Terzi, and Onar (2011), in a single-blind design, examined the impact of 6 months of piracetam given after ischemic stroke causing aphasia and found no benefit across any of the primary language or disability outcome measures, although subjects receiving piracetam showed improvement in auditory comprehension ($P = 0.023$). Thus, there were signals for efficacy in three out of four trials, three of which were relatively small (less than 25 active subjects each) and were thus likely underpowered to see small differences between groups.

85.4.5 Human Studies: Memantine

Memantine is a noncompetitive NMDA-receptor antagonist currently approved for the treatment of Alzheimer disease. A single trial has been performed examining the efficacy of memantine to treat chronic aphasia due to stroke. Berthier et al. (2009) found that 20 mg daily of memantine for 16 weeks, in the absence of SLT, produced enhanced performance on the WAB. Incorporation of constraint-induced aphasia therapy (CIAT) 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 it was slightly better than that of 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 WAB scores at the onset of CIAT. Given the good efficacy and tolerability profile of combination use of donepezil and memantine for Alzheimer disease (Tariot et al., 2004), and given the positive studies for both drugs and aphasia described here, it would be interesting to examine the effects of combination therapy on aphasia recovery.

85.4.6 Human Studies: Zolpidem

Zolpidem is a short-acting nonbenzodiazepine hypnotic that potentiates GABA. Although its hypnotic effects are similar to those of the benzodiazepines, it is classified as an imidazopyridine and is molecularly distinct from the classical benzodiazepine molecule. It binds to the alpha1 subunit of the type A GABA receptor, which is preferentially localized to the middle cortical layers of the neocortex when compared with other GABA A-receptor subtypes (Akbarian et al., 1995). There have been case reports documenting substantial clinical improvements in patients with deficits in arousal or awareness after receiving zolpidem (Clauss, Güldenpfennig, Nel, Sathekge, & Venkannagari, 2000; Thomas, Rascle, Mastain, Maron, & Vaiva, 1997). One recent double-blind, placebo-controlled report of one patient with akinetic mutism documented enhanced motor and language performance after the patient received 20 mg of zolpidem. This patient improved from having no speech output with placebo to having limited naming and repetition ability during the zolpidem period. The rCBF study of this patient using $H_2{}^{15}O$ positron emission tomography demonstrated increased blood flow to the anterior cingulate and orbital frontal cortices during the naming tasks (Brefel-Courbon et al., 2007). Another single, open-label case study reported the improvement in language function in an aphasic patient with a single dose of zolpidem (Cohen, Chaaban, & Habert, 2004). In this case report, an individual with nonfluent aphasia and a lesion in the left insula, putamen, and superior temporal gyrus had mild insomnia and was prescribed zolpidem, which led to sudden and unexpected improvement in her speech and naming ability. This remitted when the zolpidem wore off and was reproducible. An electroencephalography (EEG) failed to show any changes after zolpidem administration. Technetium-99 SPECT scanning demonstrated an increase in blood flow to Broca's area, left

middle frontal gyrus, left supramarginal gyrus, and the bilateral orbitofrontal and mesial frontal cortices. The commonality of increases in blood flow to the orbitofrontal cortices in both patients that had improved language ability under zolpidem administration raises the possibility that zolpidem influenced the planning or motivational aspects of language behavior in these patients. It is worth noting that these reports are reminiscent of the very early literature on aphasia pharmacotherapy, in which many single cases were reported, mostly involving sedative hypnotics (e.g., amobarbital) (Linn, 1947), suggesting cures of aphasia (see Small, 1994). As yet, no large-scale studies of zolpidem have been reported.

85.4.7 Human Studies: Vasopressin

Vasopressin is produced in the hypothalamus, is released by the posterior pituitary, and is thought to be important in mediating social behavior (Donaldson & Young, 2008) as well as behavior in multiple cognitive domains (Born, Pietrowsky, & Fehm, 1998; Kovacs & De Wied, 1994). Tsikunov and Belokoskova (2007) examined the effects of intranasal desmopressin (a V2-receptor agonist) administration in 26 patients with chronic stroke-related aphasia. This was a single cohort crossover design, and comparisons were made between active treatment periods and placebo periods that always preceded the active periods. The authors observed "good" responses (improvements on at least 3 out of 10 language tests) for 13 out of 26 subjects. SLT was not incorporated into this trial. Because placebo periods always preceded drug periods, this study is subject to a period effect. Review of their Figure 1 shows no improvement between the baseline and placebo periods, but improvement during the drug periods, suggesting minimal period effect. These data are promising and should be studied in a confirmatory trial. One intriguing factor here is the fact that V2 receptors (the probable target for desmopressin) are sparse in the adult human brain. Therefore, it is not clear if the beneficial effects seen here are due to desmopressin interacting with V1 receptors (which are expressed in the brain) or if a peripheral effect of desmopressin (e.g., hyponatremia) is responsible for the benefits. If desmopressin is, in fact, acting in the brain, and given the speculation of the role of vasopressin in social behavior, then it would be interesting to determine the degree to which the improvements in language function correlate with indices of social functioning in these patients. If vasopressin-based recovery has a different mechanism of action than "traditional" neurotransmitter-based therapy, this approach holds promise in being a nonredundant form of pharmacotherapy for subjects receiving one of these classes of drugs.

85.4.8 Drugs to Avoid

If certain pharmacological manipulations have the potential to improve language outcomes in aphasic patients, then it is likely that other manipulations may worsen or delay recovery. Early studies of the inadvertent pharmacological interference with aphasia recovery suggested that haloperidol and hydrochlorothiazide diuretics were associated with worse language outcomes after aphasic stroke (Porch & Feeney, 1986; Porch et al., 1985). Another early report noted that several drugs that impair recovery in experimental stroke (e.g., drugs that affect catecholamine or GABA systems) are commonly given to stroke patients for coincident medical problems (Goldstein, 1993). This led to a formal retrospective (chart review) study of patients using these specific drugs at the time of their strokes (Goldstein, 1995). A total of 96 patient records were reviewed and patients were grouped regarding whether they were using one or more of the following drugs: clonidine, prazosin, any dopamine receptor antagonist (e.g., neuroleptics), benzodiazepines, phenytoin, or phenobarbital. Statistical analysis revealed that although patient demographics and stroke severity were similar between groups, motor recovery time was significantly shorter in the group not using one of these drugs.

Several other drugs have been associated with language difficulties of one type or another and in one context or another. Certainly, the effects of anticholinergic medications on memory function (Koller et al., 2003; Sherman, Atri, Hasselmo, Stern, & Howard, 2003; Taffe, Weed, & Gold, 1999) would suggest avoiding agents with these effects. Anticonvulsant medications, notably vigabatrin and topiramate, have potentially serious cognitive effects, including causing or exacerbating aphasia (Gil & Neau, 1995; Jambaqué, Chiron, Kaminska, Plouin, & Dulac, 1998; Wong & Lhatoo, 2000). Topiramate appears to occupy a unique niche in its ability to produce cognitive disturbances, often manifesting as aphasia. Mula, Trimble, Thompson, and Sander (2003) found word-finding difficulty in 7.2% of more than 400 patients with epilepsy while using topiramate, and a case study demonstrated reversible focal left frontal hypoperfusion and motor aphasia in a seizure patient using topiramate (Cappa, Ortelli, Garibotto, & Zamboni, 2007). Language disturbances have been observed in migraine patients using topiramate as well. Coppola et al. (2008) reported that 26.7% of migraine patients in their clinic who were treated with topiramate had some form of language disturbance compared with 0% for patients using other prophylactic therapy (and matched for headache syndrome severity). These studies do not specifically address the ability for

topiramate or other anticonvulsants to alter the recovery from a lesion in the language network. Given the importance of SLT on language recovery, it is likely that topiramate would interfere with the ability of patients to optimally participate in SLT, and therefore it should be avoided.

85.5 CONCLUSION

Existing studies on pharmacological approaches to the treatment of aphasia do not yet paint a clear picture to guide current therapy. Nonetheless, there are increasingly reliable data suggesting a potential beneficial effect potentiation of catecholaminergic transmission on animal motor recovery and aphasia rehabilitation. The data are also promising for drugs that potentiate acetylcholine, as well as for compounds in which the scientific rationale and mechanisms are less clear, such as memantine, and vasopressin. Importantly, cholinesterase inhibitors and memantine have a long track record of safe use in elderly populations with cardiac comorbidities, suggesting few safety concerns about the use of these drugs. 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 few data demonstrating an impact of drug therapy on quality of life or functional outcome measures. Further, despite the common practice in most chronic diseases to use multidrug 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 in any depth.

In most cases, drug efficacy has only been seen when coupled with active SLT, which was strongly predicted by the animal literature. SLT is likely the "behavioral engine" that drives pharmacological responses (Nadeau & Wu, 2006). Therefore, pharmacotherapy should not be used as a substitute for speech therapy, and any biological intervention should be used only in concert with individually tailored behavioral therapy, preferably carefully designed adaptive learning approaches. 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. Further, aphasic patients have a host of comorbidities, such as hypertension, depression, seizures, behavioral disturbances, and others, and they are often using other medications for these. To ensure maximal recovery of language function, it will be important to balance the need for each of these medications with their potential to worsen or delay language recovery and to seek alternatives when they exist. Finally, it should be noted that advances in imaging technology in both animals and humans will make it easier to directly translate findings from rodent studies into human study design, permitting development of novel therapeutics in the future.

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