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Translational Research in Aphasia: From Neuroscience to Neurorehabilitation

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SUPPLEMENT

Purpose: In this article, the authors encapsulate discussions of the Language Work Group that took place as part of the Workshop in Plasticity/NeuroRehabilitation Research at the University of Florida in April 2005.
Method: In this narrative review, they define neuroplasticity and review studies that demonstrate neural changes associated with aphasia recovery and treatment. The authors then summarize basic science evidence from animals, human cognition, and computational neuroscience that is relevant to aphasia treatment research. They then turn to the aphasia treatment literature in which evidence exists to support several of the neuroscience principles.
Conclusion: Despite the extant aphasia treatment literature, many questions remain regarding how neuroscience principles can be manipulated to maximize aphasia recovery and treatment. They propose a framework, incorporating some of these principles, that may serve as a potential roadmap for future investigations of aphasia treatment and recovery. In addition to translational investigations from basic to clinical science, the authors propose several areas in which translation can occur from clinical to basic science to contribute to the fundamental knowledge base of neurorehabilitation. This article is intended to reinvigorate interest in delineating the factors influencing successful recovery from aphasia through basic, translational, and clinical research.

KEY WORDS: aphasia, rehabilitation, plasticity

The empirical study of aphasia treatment has a short history, spanning only the past several decades. To date, the primary focus of this research has been to determine the therapeutic value of behavioral intervention in the recovery of language impairment due to acquired brain damage. Early studies typically examined the value of language stimulation procedures that were intended to improve overall language performance in individuals with aphasia (e.g., Basso, Capitani, & Vignolo, 1979; Shewan & Kertesz, 1984; Wertz et al., 1981). The primary question of interest was whether aphasia treatment improves language ability. More recently, aphasia treatment studies have investigated the effects of specific treatments for certain language deficits. These include studies that involve between-groups and/or within-group comparisons, as well as studies using single-participant controlled experimental designs. For example, researchers have investigated the effects of treatments guided by psycholinguistic, cognitive neuropsychological, and other models of language for oral and written naming (Beeson & Hillis, 2001; Nickels, 2002; Raymer & Rothi, 2001; Rose, Douglas, & Matyas, 2002), sentence production and comprehension (Marshall, 2002; Mitchum & Berndt, 2001; Thompson & Shapiro, 2005), and other language impairments. Studies have examined the use of computer technology to improve language behaviors (Petheram, 2004; van de Sandt-Koenderman 2004; Weinrich,

Boser, McCall, & Bishop, 2001; Wertz & Katz, 2004). Other studies have been directed toward the use of alternative communication strategies, such as gesture, drawing (Lyon, 1995), supported conversation methods (Kagan, Black, Duchan, Simmons-Mackie, & Square, 2001), and the pragmatics of communication (Holland & Hinckley, 2002), investigating their effects on functional communication abilities. Additionally, studies have examined effects of treatment provided in a group setting (Elman & Bernstein-Ellis, 1999; Wertz et al., 1981). In addition to behavioral studies, researchers have undertaken studies examining the effects of various pharmacological agents to promote recovery from aphasia (Shisler, Baylis, & Frank, 2000; Small, 2004; Walker-Batson et al., 2001).

A review of the literature today yields about 800 studies of aphasia treatment, albeit not all have included the proper controls for internal validity purposes (see Thompson & Shapiro, 2005). Qualitative reviews of the accumulated research have led researchers to conclude that behavioral intervention promotes language recovery in adults with aphasia. In general, patients who receive treatment improve their language ability to a greater extent than those who do not, and the improvement noted is significantly greater than the effects of spontaneous recovery alone (e.g., Holland, Fromm, DeRuyter, & Stein, 1996). To estimate the weight of this evidence in a quantitative manner, meta-analyses of treatment outcomes studies have also been completed (Robey, 1998; Whurr, Lorch, & Nye, 1992). Such analyses are necessarily restricted to those studies that provide adequate quantitative information, which appears to be approximately one fifth of published reports. Meta-analysis has confirmed that aphasia treatment, in general, is effective compared with spontaneous recovery alone. The extent to which different types of treatment are effective for different forms of aphasia and different language behaviors has not been thoroughly evaluated through meta-analysis, however.

The research foundations for the neurorehabilitation of language remain only partially studied, however. Most previous research has been in the form of preliminary Phase 1 clinical trials examining the influence of particular treatments for impaired language behaviors as measured by performance on various language tests (for reviews see LaPointe, 2005; Murray & Clark, 2006). Less well investigated is the effect of aphasia treatment for functional use of communication. Also less thoroughly examined is whether behavioral treatments may be enhanced by pharmacologic intervention.

Neurorehabilitation research, including aphasia treatment research, has been influenced by several bodies of basic research in the neurosciences and cognitive sciences. One line of research uses animal models to study rehabilitation following brain injury (for a review, see the accompanying article by Kleim & Jones, 2008). Neurorehabilitation methods also have begun to reflect findings pertaining to the principles of learning and memory generated by studies that incorporate computer simulations and examine performance of healthy individuals. What is too often missing, however, is the bridge between basic and clinical research perspectives. Recognizing the importance and need for translational research from basic science to clinical science, the National Institutes of Health, as part of its Roadmap initiative, has instituted efforts to support translational research that encourages greater interaction between basic and applied rehabilitation scientists. In a recent forum of neuroscience and clinical speech pathology researchers sponsored by the Department of Veterans Affairs Brain Rehabilitation Research Center, Gainesville, Florida, and the University of Florida Department of Communication Sciences and Disorders (BRRC/UF), presentations and discussion focused on the potential for greater interaction between basic and applied rehabilitation scientists. The purpose of this article is to summarize those discussions and to promote renewed efforts at research along the continuum from basic science to translational studies to applied clinical trials in aphasia rehabilitation. We start with a description of neuroplasticity and evidence for neural changes associated with aphasia recovery and treatment. We then highlight a subset of the principles set forth in the companion article by Kleim and Jones (2008) that have particular relevance to aphasia treatment. We review literature from animals, human cognition, and computer simulations that serve as a background to an ensuing discussion of aphasia treatment research addressing several principles of neurorehabilitation. Ultimately, we propose a framework that might potentially guide future research efforts in neurorehabilitation and promote translational research initiatives in aphasia rehabilitation.

Neuroplasticity and Aphasia Recovery

A fundamental principle underlying the research discussed in this review is that the brain, regardless of age, is flexible and capable of change; that is, it has the capacity for structural and functional plasticity throughout the human life span. Plasticity underlies normal processes such as development, learning, and maintaining performance while aging, as well as response to brain injury. Plastic changes may be adaptive, as we expect from therapy, or maladaptive, as when an individual loses function from failure to use a skill (Kleim & Jones, 2008). Neuroimaging technologies have advanced research that addresses challenging questions regarding the neural mechanisms of aphasia recovery. Neuroimaging studies have provided evidence indicating a differential

contribution of neural mechanisms depending on the stage of aphasia recovery. Recovery of language function in the subacute stage following brain damage is aided by a neurophysiological process associated with spontaneous recovery. Left hemisphere brain regions involved in language function rendered temporarily dysfunctional by brain damage (most commonly, stroke) contribute to early recovery (Cappa et al., 1997; Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999). This physiological restitution may be complemented by reorganization of brain function, the more likely mechanism of change, particularly at later stages of aphasia recovery. In general, neuroimaging studies provide evidence for two mechanisms of functional reorganization of language in aphasia: (a) recruitment of residual left hemisphere structures that may have been premorbidly involved in language function and (b) recruitment of right hemisphere regions, typically homologous to left hemisphere language areas (Thompson, 2004). Recruitment of residual perilesional left hemisphere regions for recovery has been documented in functional imaging studies in patients with aphasia and other neurogenic communication disorders (Pataraia et al., 2004; Price et al., 1998; Rosen et al., 2000; Weiller et al., 1995). In addition to involvement of spared regions within the left hemisphere language network, a shift of language function to right hemisphere regions has also been documented in individuals with aphasia (Papanicolaou et al., 1988; Weiller et al., 1995). The respective contributions of left and right hemisphere changes are not well understood. Some researchers suggest that recovery supported by the right hemisphere may be less complete in comparison to that associated with left perilesional areas (Belin et al., 1996; Karbe et al., 1998; Kurland et al., 2004; Winhuisen et al., 2005), and others suggest that right hemisphere changes may not be responsible for long-term recovery, and may even be maladaptive (Price & Crinion, 2005). Whether patients develop intrahemispheric left hemisphere reorganization or atypical right hemisphere dominance may be influenced by factors such as the age of lesion onset or etiology of the lesion (Pataraia et al., 2004).

Research in neuroplasticity associated with aphasia has primarily focused on natural recovery processes, less commonly controlling for or manipulating the effects of behavioral treatment. Several case studies have examined changes associated with behavioral treatment. These studies provide promising evidence that functional brain reorganization underlies language improvement associated with specific treatment (Adair et al., 2000; Belin et al., 1996; Cornelissen et al., 2003; Legar et al., 2002; Musso et al., 1999; Pulvermüller, Hauk, Zohsel, Neininger, & Mohr, 2005; Small, Kendall Flores, & Noll, 1998; Thompson, 2000; Vindiola & Rapp, 2005; Weirenga et al., 2006). In addition to replicating these initial findings, more research is needed to explore how other stroke recovery factors (e.g., lesion size and location, age, type of language deficit) might influence treatment-related neural reorganization (Cramer & Bastings, 2000). In addition to the neural correlates of specific language changes, research is needed to explore neural reorganization and language use during social communication. Finally, with respect to evidence gleaned from imaging studies, researchers and clinicians must keep in mind the advice of Shih and Cohen (2004): Before we ascribe too much significance to activation maps, we need to answer basic questions such as the specific functional role of activated regions, their contribution to task performance or functional recovery, and their significance in terms of the activity they reflect (i.e., excitatory, inhibitory, both; p. 1773). For example, it has been suggested that right hemisphere contributions to aphasia recovery may reflect recruitment of attention, memory, or executive functions to support language recovery rather than restoration of language functions per se (e.g., Crosson et al., 2005).

In summary, a growing body of neuroimaging research indicates a significant relation between neuroplastic changes and language recovery. Thus, it suggests that a major purpose of rehabilitation is to maximize neural plasticity and lead to functional communication gains. To this end, researchers have attempted to explore conditions that maximize gains following aphasia treatment. The aphasia literature has been influenced by studies within the basic sciences that have dissected the conditions and influences on rehabilitation outcomes following neurological impairments.

Basic Science Evidence for Experience-Dependent Plasticity

Several lines of evidence contribute to the science of rehabilitation. Many studies incorporate animal models to explore conditions influencing recovery from brain injury. Such studies often focus on motor and sensory functions, though some studies examine recovery in cognitive domains such as spatial memory and object recognition (e.g., Dahlqvist, Ronnback, Bergstrom, Soderstrom, & Olsson, 2004). Until the necessary translational research is done, researchers can only make inferences that the same principles of recovery are relevant to language functions. Evidence from healthy individuals and computer simulations also contribute to our understanding of principles of rehabilitation, including specific examples in the language domain. From this basic science literature, Kleim and Jones (2008) entertain several fundamental experience-dependent training principles that influence neural plasticity and successful recovery from neural lesions. Extensive reviews of the neuroscience literature as it applies to aphasia recovery, in

particular, have been provided elsewhere (Keefe, 1995; Turkstra, Holland, & Bays, 2003). In this section, we highlight a subset of those principles to illustrate several basic science applications that have been particularly relevant to research initiatives in aphasia treatment that we explore in a later section.

Timing of Treatment Delivery

One of the most provocative findings from animal research is that intensive intervention early after injury may adversely affect recovery (Kleim, Jones, & Schallert, 2003; Woodlee & Schallert, 2004). Schallert, Kozlowski, Humm, and Cocke (1997) observed that two opposing processes occur during recovery: facilitative neural compensation (e.g., via reorganization of synaptic networks) and secondary neurodegenerative processes induced by the injury. Both of these processes may continue for hours or days postinjury and have been hypothesized to influence stroke recovery (Seisjo, 1992a, 1992b). For example, Schallert et al. explored whether compensatory behavioral strategies may exacerbate secondary injury when provided early postinjury. They found that lesions of the rat sensorimotor cortex induced positive changes in contralateral brain regions (e.g., increased dendritic branching) only if the animal was free to use both the affected and unaffected limbs. In other words, there was reorganization of brain function as compensation. However, if the animal was forced to use the weak limb (which is akin to constraint therapy approaches in humans), lesion size actually increased, an example of secondary neurodegenerative injury, and more severe and persistent symptoms were observed. Early exposure to enriched environments, particularly when paired with intense motor training, has been found to have detrimental effects on neuroplasticity mechanisms within both cortical and hippocampal brain regions (Farrell, Evans, & Corbett, 2001; Kleim et al., 2003). Importantly, this pattern of physiological response does not persist for long after injury. Schallert and colleagues (1997; Woodlee & Schallert, 2004) have reported no effect of weak limb overuse that occurs after the first 7–14 days postinsult. The timing of treatment, however, appears to interact with other variables such as lesion site. For example, weak limb overuse during the acute stages of recovery did not negatively affect either lesion size or behavioral symptoms in rats when stroke affected subcortical versus cortical brain regions (Woodlee & Schallert, 2004).

From a clinical perspective, Schallert and colleagues (1997) concluded that, in the acute stage after injury, "behavior, including neurological assessment, might affect neural events … [as] the behavioral tests themselves might alter the process of recovery" (p. 236). Thus, timing of intervention apparently is critical. It remains to be established what period should be considered "acute" in humans to help guide clinicians regarding when they can prescribe more aggressive treatment aimed at reinstituting impaired functions. This is a very important question, given that these findings are basically from rats, whose life spans are considerably shorter than human life spans. That is, the first 7–14 days postlesion in rats may in fact constitute a far longer time period than that amount of time in humans. In contrast, intensive intervention in the chronic stage is effective not only at improving function, but also at preventing loss of function, in both animals and humans.

Use It or Lose It

Animal research has shown that the failure to participate in rehabilitation has adverse effects on recovery. More than 30 years ago, Taub and colleagues (see summaries in Taub et al., 1994; Taub, Uswatte, & Elbert, 2002) demonstrated that nonhuman primates learned to avoid using an injured limb based on negative experiences in the early phase after an injury, and that this early "learned nonuse" prevented later functional recovery of the affected limb. Eventually, the animals permanently ceased to attempt to use the injured limb. Taub et al. found, however, that if the animal was forced to use the injured limb (typically by binding the intact limb), the function of that limb improved over time.

Research by Feeney and colleagues (Feeney, Gonzalez, & Law, 1982; Feeney & Sutton, 1987, 1988) yielded findings that are an interesting complement to those of Schallert et al. and Taub et al. Feeney et al. studied the effects of physical and chemical restraints on recovery from stroke, primarily in cats. They found that both types of restraints retarded recovery, whereas animals that received "rehabilitation" (beam-walking practice) had significantly faster and better recovery of function. In addition to supporting the benefits of intervention, this finding raised questions about the use of chemical restraints such as Haldol in the acute and subacute stages after neural injury.

Recently, social restraints have also been found to have negative effects on neurological and behavioral recovery. Craft and colleagues (2005) examined the effects of the presence or absence of social interaction on lesion size, weak limb use, and stress levels (as measured by concentrations of certain hormones and protein in blood samples) in rats with middle cerebral artery stroke. Although the findings varied slightly depending on the gender of the rats, rats that were housed with an unlesioned rat demonstrated greater decreases in their lesion size and stress levels and increases in their use of their weak limb compared with rats that were isolated during acute recovery from stroke.

Generalization and Transfer of Treatment Effects

When an animal undergoes behavioral stimulation, many changes occur at the neuronal level (see review in Kolb, 1995). These include increases in the number and density of synapses, dendritic length, and synapse size. The results of several experiments suggest that these changes may allow animals to improve performance on tasks that are not specifically trained. That is, improvements on one task may generalize to novel, related tasks. For example, Kolb reported that rats trained on a task with one paw showed increased dendritic patterns in homologous regions in both hemispheres. Moreover, these changes were similar to the changes observed in rats trained with two paws. Kolb and colleagues suggested that experience may "prime" the brain for future learning. This is an intriguing notion, as it suggests that engagement in the therapy process itself might increase the probability of gains beyond the behavior trained.

The complexity and richness of the training environment can also influence the extent of the treatment effects. For example, Komitova, Zhao, Gido, Johansson, and Eriksson (2005) compared the effects of an enriched environment (e.g., cages that include lots of objects, chains, swings, etc. of different sizes and materials that are varied over time) with that which encouraged only voluntary running (i.e., cages that include a running wheel only) on the neural and behavioral poststroke recovery of adult rats. Rats exposed to the enriched environment demonstrated significant behavioral gains (i.e., ability to traverse a rotating pole) and positive neural changes in ipsi- and contralateral neural regions. In contrast, rats in the running wheel cages showed no significant functional improvements and less neuroplasticity change than had been anticipated. These findings as well as those from other studies comparing the effects of training complex/skilled behaviors versus simple motor skills (e.g., Ding, Clark, Diaz, & Rafols, 2003) suggest that greater functional outcomes and enhancement of positive neuroplastic changes are more likely when rehabilitation incorporates complex tasks and/or environments.

Influence of Repetition and Intensity of Treatment

Pascual-Leone, Wassermann, Sadato, and Hallett (1995) showed that repetition is important in maintaining changes in the brain and their corresponding functional benefits. They found that changes observed in the cortical maps of blind individuals who were proficient Braille readers and used Braille at work depended on whether the participants had been working for a 6-hour period or had taken the day off work. This result may be familiar to readers who perform skilled arts or sports, and miss a few days of practice. From a clinical perspective, it supports the need for long-term, consistent use of a skill to maintain gains in therapy.

Woodlee and Schallert (2004) suggested that because early overuse of a weak limb can result in greater deficits, and complete disuse can also slow recovery, acute rehabilitation should be less intense and then, over time, become more "aggressive." Kleim et al. (2003) found that motor map reorganization and increased synapse formation occurred only after more extended training of skilled/complex reaching in adult rats. That is, neural differences between rats that underwent skilled versus unskilled reaching training became apparent only after 7–10 days of training. The rats receiving training in skilled reaching showed the most dramatic improvements in skilled reaching after just 3 days of training; after that they continued to show behavioral improvements, but the rate of improvement was much slower. Therefore, the implication of this work is that patients may need to be trained beyond acquisition of a complex behavior (e.g., any language behavior) if we hope to induce neural changes. Without the essential translational research, however, it is unknown whether these findings can be extended to language or even motor abilities in humans.

A large literature on memory and learning, particularly in motor learning tasks, conducted in healthy individuals provides another body of evidence relevant to the intensity of training schedules. A meta-analysis of 63 studies by Donovan and Radosevich (1999) indicated that with regard to *retention* of learning effects, the effects of practice provided in a distributed practice schedule surpass those of a massed practice schedule. The advantage reported for distributed practice was modulated by the nature of the training task, as the effect was somewhat less potent for more complex activities. This observation has implications for the training schedule used with patients in clinical settings.

Computer Models in Rehabilitation Research

In addition to animal and human models of learning, memory, and rehabilitation, computer simulations have provided a line of evidence that has influenced subsequent studies of aphasia rehabilitation. Theories and models of cognitive processes such as language were developed first on the basis of observations of human behaviors. In the past few decades, the understanding of cognition has benefited further from computer simulations of these theories and models. Computational instantiations of theories can be used to generate and test hypotheses about cognitive functions under both normal and impaired conditions. In the language domain,

computational models have been used to test theories of lexical access in word production (Dell, 1986; Harley, 1984; Levelt, Roelofs, & Meyer, 1999; McNellis & Blumstein, 2001; Plaut & Booth, 2000), word recognition (McLeod, Plaut, & Shallice, 2001), serial order mechanisms in word production (Vousden, Brown, & Harley, 2000), and, more recently, articulatory mechanisms in humans (Kello & Plaut, 2004). (See Nadeau, 2000; Nadeau & Rothi, 2004, for a detailed review.) Likewise, these models have been instrumental in furthering researchers' understanding of the nature of impairments to mechanisms of lexical access (e.g., Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Gotts & Plaut, 2002; Mikkulainen, 1997; Plaut, 2002; Rapp & Goldrick, 2000; Ruml & Caramazza, 2000) and semantic memory (e.g., Lambon-Ralph, McClelland, Patterson, Galton, & Hodges, 2001) subsequent to brain damage. Computational models have also contributed to researchers' understanding of possible mechanisms underlying recovery of language function after damage (Martin, Dell, Saffran, & Schwartz, 1994; Martin, Saffran, & Dell, 1996; Plaut, 1996; Schwartz & Brecher, 2000). With respect to treatment, computational models have generated hypotheses about language learning (Plaut & Kello, 2002) and the role of short-term memory processes in word learning (Gupta & MacWhinney, 1997). Additionally, some researchers are beginning to use computer models to examine processes exploited in treatment tasks such as priming (Plaut & Booth, 2000), and others have generated predictions about interfering and facilitating effects of priming with semantically or phonologically related words on lexical access (Martin, Fink, Laine, & Ayala, 2004).

Item characteristics such as concreteness and frequency are known to influence normal and impaired lexical access. Computational models have been used to demonstrate these effects (Martin et al., 1996; Plaut & Shallice, 1993) and to account for them within cognitive theory. Moreover, computational studies have informed researchers about how the characteristics of stimuli that are used in training can maximize generalization to untrained items. Plaut (1996) demonstrated in his connectionist model that greater relearning of a semantic category occurred when training included both typical and atypical members of that category. This finding was tested by Kiran and Thompson (2003) in their study of word retrieval treatment in aphasia. These findings challenge conventional wisdom with a new logic that in hindsight makes good sense: Training more complex members highlights an array of features associated with the category, prototypes as well as those of atypical members; training typical items highlights only prototypical features. Plaut's computer model, then, revealed something about a principle of learning and relearning that may be translated directly to neurorehabilitation.

As another example, Gordon and Dell (2003) used a computer simulation to examine the influence of syntax and semantics in lexical production for nouns and verbs. The computer was trained to produce sentences with either heavy or light verbs (i.e., verbs that vary according to the number of semantic features that make up the verb; Breedin, Saffran, & Schwartz, 1998). Ultimately, Gordon and Dell found that semantic features were more important for learning to produce heavy verbs and nouns, whereas syntactic features influenced production of light verbs and function words. Gordon (2005) used these findings to motivate a study examining contrasting treatments for verbal production in a patient with aphasia.

Clinical Aphasia Evidence for Principles of Experience-Dependent Plasticity

Within the aphasia treatment literature, studies have addressed several of the variables discussed earlier that are hypothesized to influence treatment outcomes. Among these are the intensity and timing of treatment delivery. Other work has focused on variables related to generalization, or transfer, of treatment effects to untrained material. As shown next, a fair amount is known with regard to some of these influences on aphasia treatment outcomes. The picture is far from complete, however.

Timing of Treatment Delivery

It is a long held notion in aphasia rehabilitation that treatment should be provided as early as possible following the aphasia-inducing event, suggesting that treatment provided in more chronic stages of recovery is less likely to be effective. Wertz and colleagues (1986), however, found that a group of participants who delayed entry to their aphasia treatment protocol by 3 months caught up with a group that instituted treatment in the subacute phase of aphasia recovery. In a meta-analysis, Robey (1998) examined the magnitude of treatment effect sizes relative to the timing of treatment and found, however, that treatment begun during the acute period (before 3 months postonset) resulted in almost twice the effect size of spontaneous recovery (1.15 vs. 0.63) and that the effect size of treatment initiated during the subacute period (between 3 and 12 months postonset) was small, but greater than that for untreated individuals (0.57 vs. 0.34). In addition, treatment initiated during the chronic stage (after 1 year postonset) showed an effect size similar to that during the subacute period and was notably larger than that for untreated individuals (0.66 vs. 0.05). These data indicate that early treatment may be maximally beneficial but that later

treatment also impacts language ability and use. In Robey's meta-analysis, the acute phase encompassed a fairly broad 3-month time frame. Studies examining recovery in aphasia show that most spontaneous recovery actually occurs within the first 2 months post–aphasia onset (e.g., Holland, Greenhouse, Fromm, & Swindell, 1989). Although treatment effects are greatest in acute stages of aphasia recovery, several studies have reported remarkable gains in language abilities many years following aphasia onset (e.g., Kendall et al., 2006).

Use It or Lose It?

Taub and colleagues (Taub et al., 1993, 1994) replicated the animal research on forced use to overcome "learned nonuse" in studies of hemiparetic human stroke patients. Based upon the notion that the potential rehabilitation of the affected limb is detrimentally influenced by the compensatory use of the unaffected limb through a process of learned nonuse, constraint-induced movement therapy (CIMT) has been shown to result in improved bimanual performance in some patients with chronic poststroke hemiplegia (Kunkel et al., 1999; Liepert et al., 2000; Taub, Uswatte, & Pidikiti, 1999). The key principles of CIMT are massed practice, constraint of the unaffected limb with forced use of the affected limb, and behavioral shaping of the response. These principles have been applied to the rehabilitation of chronic aphasia as well by Pulvermüller and colleagues (2001). Individuals with chronic aphasia received intensive massed practice with oral language over a 2-week period, restricting responses only to spoken language in a variety of interactive communication tasks. This intensive training was associated with significant improvements on standard tests and other and self-ratings of communication in daily living. The increased benefit that constrained therapy yielded relative to conventional therapy, however, was confounded by differences in the intensity with which the two treatments were delivered (i.e., constraint therapy was provided more intensively than conventional therapy).

Maher et al. (2003) conducted a partial replication of the Pulvermüller et al. (2001) study that attempted to control for intensity. In the Maher et al. study, 4 participants underwent constraint-induced language therapy (CILT) and a comparison group of 5 participants underwent PACE (promoting aphasics' communicative effectiveness) therapy (Davis & Wilcox, 1985) using the same stimulus materials and treatment schedule as the CILT group. Whereas both groups showed some change, there were greater treatment gains observed and maintained in verbal measures in the CILT group compared with the PACE group. The PACE group, in contrast, increased use of nonverbal behaviors. This suggests that the active components of CILT cannot be attributed to the intensity of the intervention alone and supports the notion of forced use of verbal behaviors in rehabilitation. The importance of continued use is suggested in a further study by Meinzer, Djundja, Barthel, Elbert, and Rockstroh (2005), who evaluated the effects of two forms of constraint-induced therapy. One form was similar to that used in previous research, and the other included writing activities and training of daily communication activities with the assistance of family members. Positive outcomes on standard tests and patient and family ratings were observed following administration of 10 days of treatment (total of 30 treatment hours) for both groups, and these gains were maintained at a 6-month follow-up. Moreover, greater gains on patient and family ratings were observed for patients who had received treatment that involved family members who presumably continued to promote use of the speech modality after therapy had been terminated.

Generalization, or Transfer, of Treatment Effects

Many studies in the aphasia treatment literature have addressed generalization of treatment effects to untrained language behaviors. Results of this work have been mixed. Whereas some studies have shown little generalization, others have shown positive effects of treatment on the language behaviors tested for generalization. One principle that has resulted from this work is that generalization is most likely to occur to a language behavior that is similar to the trained language behavior. For example, in treatment of naming impairments, training items from a particular semantic category results in greater generalization to untrained items from the same class than to untrained items from a different semantic category (e.g., Kiran & Thompson, 2003; see also Nickels, 2002, for review). In the domain of sentence production and comprehension treatment, generalization is most likely to occur to untrained sentences that are syntactically related to trained sentences (Thompson & Shapiro, 2005). These results likely reflect the organization and processing of language in which similar processing routines and representations are utilized for similar language behaviors. Thompson, Shapiro, Kiran, and Sobecks (2003) showed that the complexity of language material used in treatment also impacts generalization (i.e., the complexity account of treatment efficacy [CATE]). Although counterintuitive, training complex language material can result in improvements in less complex, untrained language. In contrast, training simple material has little effect on mastery of more complex material. Importantly, this complexity effect occurs only when the trained and untrained material are linguistically related

(e.g., training complex sentences that involve certain syntactic constructs results in generalization only to simpler sentences that involve the same syntactic constructs). Furthermore, influenced by the Plaut (1996) computer simulation mentioned earlier, Kiran and Thompson (2003) extended the complexity effect to the semantic domain and demonstrated improved word retrieval by training atypical members of a category (e.g., birds: ostrich) versus typical members (e.g., robin). Overall, aphasia studies reporting generalization of training effects to untrained language behaviors complement the findings in the animal literature reporting transfer of training effects to untrained behaviors.

Intensity of Treatment

The notion that providing intense treatment (i.e., several hours a day or week) enhances recovery to a greater degree than distributed practice (i.e., 1 or 2 hr a week) was a basic tenet of Schuell et al.'s approach to treatment in the 1960s (Schuell, Jenkins, & Jimenez-Pabon, 1964). This issue has received recent attention in the aphasia literature, albeit few controlled studies have directly compared intense versus distributed treatment schedules. With respect to word retrieval in aphasia, Hinckley and Craig (1998) reported that intensive training (>20 hr per week) led to significant improvements in a standardized word retrieval measure as compared with a nonintensive training protocol (3 hr per week). The intensity of treatment (when reported) was examined in the extant literature by Robey (1998). Results showed that the more intense the treatment, the greater the change. In general, it appears that 2 or more hr per week of treatment result in greater change than treatment delivered at a lower intensity ($\leq$1.5 hr per week). Bhogal, Teasell, and Speechley (2003) reviewed 10 studies of aphasia treatment meeting selection criteria and found that those studies reporting significant treatment effects provided on average 8.8 hr of therapy per week for 11.2 weeks. In contrast, those without significant treatment effects provided an average of 2 hr of therapy per week for 22.9 weeks. Although the positive gains observed following constraint therapy cannot be attributed solely to intensity (Maher et al., 2003), these studies provide additional support for the importance of treatment intensity as well. Individuals in the intense PACE comparison group also improved, suggesting that intensity may be an active factor in a positive treatment response.

Other Factors Affecting Treatment Outcomes

We have highlighted evidence associated with only a subset of the principles of use-dependent plasticity reviewed by Kleim and Jones (2008). Other factors influence aphasia treatment outcomes, such as the personal relevance (i.e., salience) of targeted skills and stimuli, the type of treatment experience, participant factors such as lesion location, cognitive status, motivation, age, overall health status, and the interactions among these factors. With regard to each principle, however, questions remain to be formulated and examined to determine optimum conditions to maximize neural plasticity and aphasia recovery.

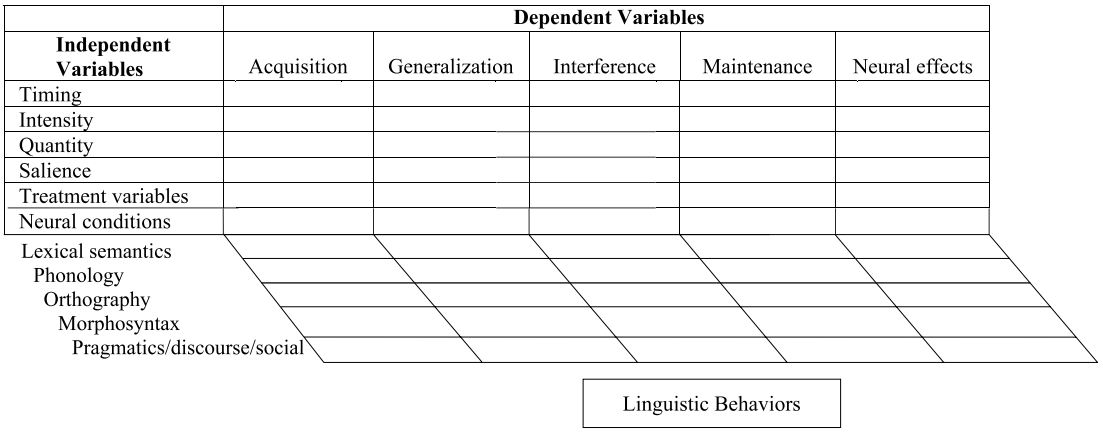
Conceptual Framework

An emerging literature in the basic sciences of neurorehabilitation in animals, healthy humans, and computational models support several principles that play active roles in influencing treatment outcomes. The principles outlined by Kleim and Jones (2008) ultimately suggest several directions for additional basic and applied treatment research. In reviewing the principles of neurorehabilitation, it is worth noting that terminology at times tends to vary across disciplines (e.g., neuroscience vs. speech-language pathology). Table 1 specifies terminology and a set of working definitions that serve as a backdrop for the following discussion. In this section, we present a framework to facilitate the discussion of these findings in a manner that we hope will be useful in planning future research. Central to our proposed framework is the organization of a number of the principles and concepts that have figured prominently in the basic science literature into the categories of *dependent* and *independent* variables. That is, several principles of use-dependent plasticity can be viewed as factors that can be manipulated as independent variables within rehabilitation experiments. Other principles more directly translate to outcome variables or dependent variables within experiments. A discussion of these principles of use-dependent plasticity in the BRRC/UF Language Work Group led to the development of a conceptual framework within which rehabilitation research questions might be systematically investigated. A schema delineating the interplay among these independent and dependent variables is represented in Figure 1. For the sake of this discussion, we have added a third dimension to our framework representing the variety of linguistic behaviors that may be the target of treatment for individuals participating in neurorehabilitation for language impairments. The schema could certainly be expanded in all directions and can be readily adapted for a multitude of target behaviors in cognitive, motor, and sensory realms. This framework provides an organizational scheme for systematically reviewing the literature and identifying areas of research lacking empirical support and needing further investigation.

Table 1. Definitions.

	Definition
Independent Variable	
Timing	The temporal relation between insult and intervention. Timing can vary from the acute immediate effects of neurologic disease to chronic stages of recovery.
Quantity (repetition)	The total number of intervention units, which varies along a numerical continuum from few to many opportunities for practice.
Intensity	The frequency of intervention unit per time unit. Intensity is usually reported as the number of hours of intervention provided within 1 week. Intensity can vary from intensive, massed practice (e.g., 20 hr of treatment per week) to a distributed, less intensive schedule (e.g., 2 hr of treatment per week).
Salience	The perceived value or relevance of the experience to the participant.
Treatment variables (experience-specific training)	Any of the behavioral and/or neural manipulations that take place during the rehabilitation activity. Some of the techniques are intended to restore functions in a manner compatible with normal functioning, whereas others attempt to compensate for impaired functions in a fundamentally different way.
Neural conditions	Participant characteristics (e.g., lesion site and size, participant age) that have the potential to influence treatment outcomes. Such characteristics are often used as grouping variables to define subsets of participants with common attributes.
Dependent Variable	
Acquisition	The change of behavior as a result of intervention. This is measured throughout the treatment process and/or at the completion of training.
Generalization	*Response generalization* is the influence of the intervention for other untrained behaviors. The untrained behaviors may or may not have some type of systematic relation to the untrained behavior. *Stimulus generalization* is the use of the acquired behavior in contexts or conditions other than those in which treatment occurred. Often such contexts include situations in which the behavior is used in a meaningful way apart from the training context, discourse sampling conditions, or functional environments.
Interference	The negative impact of one behavior on the acquisition of another behavior. That is, improvements in one behavior tend to undermine the potential for improvements in other similar behaviors.
Maintenance	The stability of an acquired behavioral change over time in the absence of continued intervention. The term *retention* may also be used to refer to the same concept.
Neural effects (plasticity)	The observed changes in neural activity associated with an intervention. These may include perilesional regions or regions, often homologous, in the contralateral hemisphere.

Figure 1. Proposed conceptual framework.



Implications for Aphasia Treatment Research

This conceptual framework might potentially be used to guide rehabilitation research in the area of acquired aphasia. The practical implications of basic science work drive us to question some of our conventional rehabilitation practices. These become particularly important when we recognize that some of the more compelling evidence from basic science is counter to conventional intuition and general, accepted clinical practice. For example, results from basic neuroscience research suggest that treatment outcomes vary relative to the *timing* of the intervention. In the animal model, early intervention provided in an extremely intense schedule (e.g., 24 hr/day) may have a negative effect on outcome (Farrell et al., 2001; Kleim et al., 2003; Schallert et al., 1997). However, there is evidence to indicate that complete disuse may also impede recovery (Taub et al., 1994, 2002). Furthermore, early intervention might be necessary to optimize response to neurotrophins released following brain lesions (Cramer & Chopp, 2000). The adult clinical evidence suggests that aphasia treatments begun early yield larger effect sizes than those started later (Robey, 1998). Whether it is the timing of treatment or the intense schedule that led to negative outcomes in some animal studies is not clear. However, these observations bring up questions that need to be answered about the timing of aphasia rehabilitation. Moreover, there is some question about unexpected interactions with other variables at different times in recovery. Using notions developed from Woodlee and Schallert (2004), we predict that conditions that might optimize treatment outcomes in chronic aphasia might actually be less optimal in acute aphasia. Thus, specific guidelines regarding what time periods in recovery should be considered "acute" versus "subacute" versus "chronic" for the adult clinical population are needed. Furthermore, factors that have the potential to interact with timing of treatment, including site and extent of lesion, type of treatment, and the intensity of treatment need to be explored. The conceptual framework schematized in Figure 1 may facilitate the design and systematic investigation of a specific variable, like timing, to examine interactions between the time of treatment, the type of treatment provided, and the language domain affected. Research efforts are needed to identify at what stage rehabilitation (a) is most effective, (b) is not effective, and (c) might actually be harmful.

Moving down the list of independent variables represented in the conceptual framework, the need to determine optimal treatment *intensity* is certainly prompted by basic neuroscience as well as adult clinical evidence and is directly related to models of service delivery and funding for rehabilitation. Not only did treatment intensity affect skill acquisition and retention in the animal model (Kleim et al., 2004), findings reported earlier for the effect of intensity on learning in healthy individuals emphasized the advantage of distributed over massed training practice (Donovan & Radosevich, 1999). Likewise, a recent study showed that a distributed form of CIMT was effective for improving motor functions (Dettmers et al., 2005). The aphasia treatment literature, in contrast, has reported benefits of a more intensive, condensed treatment schedule. A possible explanation for these differences may relate to the period of time under study; the aphasia treatment studies tended to report results at the completion of training (acquisition), whereas the learning literature has centered on retention of learning effects. In either case, the conventional outpatient treatment schedule (i.e., 2–3 times per week) is challenged by these data.

Yet to be determined is the influence of treatment intensity across different domains of language or dependent variables. Future research needs to examine the relative effect of treatment intensities on behaviors that span domains of language and communication (e.g., semantics, phonology, orthography, morphosyntax, pragmatics/discourse/social). The conceptual framework guides the design and systematic investigation of a specific variable, like treatment intensity, to address specific questions such as the following: What are relative effects of differences in treatment intensity across domains of language? Is there a differential effect of massed versus distributed practice on the acquisition, generalization, or maintenance of a new language behavior? How do variations in treatment intensity affect neural structure and/or function? Additional studies aimed at examining the effects of treatment intensity are certainly warranted, along with an evaluation of the effects of language activities designed to complement treatment sessions (i.e., homework).

Within rehabilitation, there will be a close interplay between *quantity* (repetition) and intensity. However, the implications from basic neuroscience and computer models are that patients may require training beyond the acquisition of a complex behavior (e.g., any language behavior) for those changes to be lasting and induce neural changes (Kleim et al. 2003; Pascuale-Leone et al., 1995). The amount of repetition required for acquisition, maintenance, and generalization of various language domains, as well as to yield neuroplastic changes, needs to be explored systematically within this conceptual framework.

A number of factors that might collectively be referred to as *treatment variables* or training experiences, such as the presence of an enriched environment (Komitova et al., 2005) or the complexity of the task (Ding et al., 2003; Thompson et al., 2003), have been shown in

the basic neuroscience literature to have the potential to influence neural plasticity in fundamentally different ways. Potential sources of data on enriched contexts in humans can be found in studies of natural communication and conversation. For example, researchers investigating the efficacy of group aphasia therapy demonstrated that group "conversation" treatment was superior to unguided "socialization" in promoting language recovery in groups with chronic aphasia (Elman & Bernstein-Ellis, 1999). Whereas there is some evidence that these treatment variables influence outcomes in the adult clinical population, very little of this has been studied systematically, and this conceptual framework might be used to organize these investigations. For example, exactly what constitutes an enriched environment for humans and how does it impact language acquisition, generalization, and maintenance? Are there conditions of treatment that might actually lead to *interference* when treatment moves to other language behaviors?

Although we may accept the principle of Use It or Lose It, what kind of use is important for yielding stable, neuroplastic change? Is constraint to the speech modality necessary, or can it be combined with other nonverbal strategies and be equally effective? How does treatment complexity differ across the language domains? These same questions also apply to the independent variable of salience, which ultimately may need further refinement. Salience may have several different dimensions, including some associated with the external conditions of the treatment (e.g., lexical context, perceptual attributes of stimuli) and others with internal aspects of the rehabilitation task as implemented with a research participant (e.g., meaningfulness of the stimuli for that individual, attentional status and motivation of the participant). Through the systematic investigation of these variables, we may be able to determine the critical factors that account for much of the currently unexplained variance in treatment results observed in the clinic.

Feedback to Basic Science Efforts

We have proposed several areas in which principles of experience-dependent plasticity grounded in basic science research might be used to guide further research within aphasia treatment. It should be emphasized, however, that the interactions between basic and clinical science need not evolve in one direction only. Data emerging from aphasia research should influence research questions within the basic sciences, as well. For example, the issue of timing of treatment delivery is of great concern in aphasia. We certainly do not want to provide treatment in a time frame that actually reduces or interferes with long-term potential for recovery. To address this question, we would turn to basic neuroscience research to identify specific biological markers (e.g., within blood samples) that indicate excitotoxicity or that may index severity of injury. It may be possible to identify such biomarkers of acute, subacute, and chronic phases of recovery from brain injury in animal models that then could be explored in the human model. The ultimate goal would be to time intervention during the most favorable periods and to avoid potentially vulnerable periods.

Rehabilitation specialists are also interested in issues concerning the effects of lesion characteristics on rehabilitation outcomes, an area that also might be further evaluated in the animal model. Questions such as effects of lesion location might be examined. For example, given their contributions to learning and memory, hippocampal and basal ganglia lesions need to be explored systematically. Influences of multiple lesion sites and extent of lesions are also important topics for investigation in animal models. Aphasiologists have identified a variety of variables within the treatment context that influence treatment outcomes. For example, recent aphasia treatment studies have been interested in the influence of errorful versus errorless training (Fillingham, Sage, & Lambon Ralph, 2005, 2006) and spaced retrieval training protocols (Fridriksson, Holland, & Beeson, 2005). Such variables might be systematically manipulated in animal models to determine the nature of any neuroplastic changes that are observed and that conditions maximize neuroplastic changes.

Much of what is known about principles of neurorehabilitation comes from studies of rodents with brain lesions. The application of rodent studies to neurorehabilitation of language is necessarily limited. Studies examining birdsong in birds with brain lesions (Brainard & Doupe, 2000) may bring us a step closer to studies of language. For example, such studies might be informative about the role the auditory system plays in recovery of speech and language functions (Bolhuis & Gahr, 2006).

While animal models cannot answer questions that are specific to aspects of language, computational models of cognition and language can play an important role in future efforts to translate from animal to human models of language recovery and rehabilitation. One of the more intriguing characteristics of computational models is their ability to learn based on experience, and once that learning has been established, to be "lesioned" systematically and "rehabilitated" (Nadeau, 2000). The output of this process can then be compared with behavioral data to generate and test hypotheses related to rehabilitation. In this way, studies can examine fundamental principles of learning common to both animals and humans to behaviors shared by both populations, but not identically manifested (e.g., swallowing behaviors, memory skills), to language behaviors unique to

humans, such as spoken and written language processing. Data from aphasia treatment studies could be used to develop and implement computer simulations that might provide more explanatory power for the bases of rehabilitation effects.

From animal models to date, it seems clear that learning and relearning any behavior will likely vary depending on the timing of intervention as well as the intensity and duration of treatment. What researchers cannot learn from animal research is how such principles will interact with the content and social use of language behavior that they aim to rehabilitate in humans. Recent empirical studies (e.g., Martin, Fink, & Laine, 2004) of treatment for anomia suggest that responses to such treatment vary depending on the content of treatment (semantic vs. phonological) and source of naming impairment (semantic, phonological, or both), and that these two variables may interact with each other. Animal models cannot answer questions about aspects of language that are impaired and how they interact with recovery and relearning. Nor can they answer questions about possible interactions between intensity of treatment, stimulus type (e.g., semantic or phonological), and type of impairment (e.g., semantic or phonological). We note, however, that those sorts of questions might be addressed with computer simulations.

Recent research in errorless versus "errorful" learning provides an example of approaches to learning that might vary in their effectiveness depending on the behavior to which they are applied. Errorless learning techniques that minimize opportunities for error during the learning process have been successful in treating memory impairments (Wilson, Baddeley, Evans, & Shiel, 1994). In treatment of word retrieval and sentence production disorders, this approach has fared as well as errorful learning approaches (Fillingham et al., 2005, 2006; Maher et al., 2002). In fact, error-reducing techniques for word retrieval such as repetition priming have been found to be less effective when access to semantics is impaired (Martin et al., 2004a). Likewise, recent investigations in memory treatment suggest that the type of material to be learned can influence the relative advantage of errorless over errorful learning (Evans et al., 2000). Studies such as these indicate that researchers have much more to learn about the contexts in which errorful versus errorless learning approaches are most effective. It may be, for example, that rehabilitation of lexical–semantic processing impairment requires more errorful learning approaches, as in semantic feature analysis treatments (e.g., Boyle, 2004), which encourage the learner to generate semantic associations to a concept and, thus, stimulate deeper processing and discrimination of many features of concepts. Questions about errorless versus errorful learning can be answered in animal models with respect to some behaviors shared with humans (e.g., motor learning). However, translation of those findings directly to the domain of language might be implemented with a computational model that can test these principles in a simulation that represents language behavior. The role of computer models in translational rehabilitation research can be one of a bridge between the fundamental principles of learning that are common to both animals and humans and the manifestation of those principles in the domain of spoken and written language.

Finally, efforts also need to progress to determine links between what is known about neuroplasticity and to use this knowledge to researchers' advantage when planning patient intervention. Initial work in this direction can be seen in studies examining relations between electrophysiological measures and aphasia assessment (e.g., Marchand, D'Arcy, & Connolly, 2002). Repetitive transcranial magnetic stimulation (rTMS) has a role to play in this regard as well. In healthy individuals, the extent to which rTMS, when applied to the left hemisphere, disrupted language functions correlated with the degree of language lateralization as determined on functional magnetic resonance imaging (Knecht et al., 2002). Functional neuroimaging studies of aphasia recovery often show right hemisphere activation that some have argued is less suited to effective aphasia recovery (Price & Crinion, 2005; Winhuisen et al., 2005). As a means to promote aphasia recovery, Naeser, Martin, Nicholas, Baker, Seekins, Helm-Estabrooks, et al. (2005) and Naeser, Martin, Nicholas, Baker, Seekins, Kobayashi, et al. (2005) have applied rTMS to the right inferior frontal cortex of individuals with nonfluent aphasia and have shown improved naming abilities that have lasted several months. Questions that arise from intervention may lead back to basic studies in neuroimaging and neurophysiology to determine markers for successful recovery and rehabilitation potential.

The Future of Translational Research

Researchers in clinical aphasiology have always been appreciative of and sensitive to the principles of neurorehabilitation that emerge from the basic science literature as it applies to research in aphasia treatment and recovery. Further progress in research requires much interaction in how researchers move along a continuum from basic science developments to translational studies in humans to clinical trials. Studies in animal models of neurorehabilitation, computational simulations of aphasia, and the cognitive science work that focuses on the acquisition of complex behaviors (i.e., skill acquisition theories and approaches) are all rich sources of translational

interest to aphasiologists. Questions, concerns, and problems encountered in human clinical interactions should then lead back to motivate further basic science investigations. A productive basic science and clinical science research process, then, is interactive, integrated, and complementary. More and more researchers are recognizing this critical need for increased cooperation and integration of research endeavors. With renewed emphasis on this perspective that has been encompassed in the NIH Roadmap initiative, the future of translational research is indeed promising. Neurorehabilitation researchers, including aphasiologists, need to continue to build bridges among basic and clinical disciplines to promote a research agenda in which all researchers' treatment initiatives flourish.

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