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Psycholinguistics of Aphasia Pharmacotherapy: Asking the Right Questions

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Abstract

Background—Among the obstacles to demonstrating efficacy of pharmacological intervention for aphasia is quantifying patients' responses to treatment in a statistically valid and reliable manner. In many of the review papers on this topic (e.g., Berthier et al., 2011; de Boissezon, Peran, de Boysson, & Démonet, 2007; Small & Llano, 2009), detailed discussions of various methodological problems are highlighted, with some suggestions on how these shortcomings should be addressed. Given this deep understanding of caveats associated with the experimental design of aphasia pharmacotherapy studies (e.g., Berthier et al., 2011), investigations continue to produce inconsistent results.

Aim—In this review paper we suggest that inclusion of theory-driven linguistic measures in aphasia pharmacotherapy studies would add an important step toward elucidating precise patterns of improvement in language performance resulting from pharmacotherapeutic intervention.

Main Contribution—We provide a brief review of the clinical approaches currently used in pharmacotherapy studies of aphasia, which often lack psycholinguistic grounding. We then present ways in which psycholinguistic models can complement this approach, offering a rationale for task selection, and as a result, lead to a better understanding of treatment effects. We then follow with an example of how such an integrative approach can be implemented in studies targeting stress reduction in people with aphasia, via beta-blocking agents, as a means to augment language performance, using the psycholinguistic framework of “linguistic anxiety” outlined in Cahana-Amitay et al, 2011 as our guideline.

Conclusion—We conclude that the incorporation of psycholinguistic models into aphasia pharmacotherapy studies can increase the resolution with which we can identify functional changes.

Over the past quarter century, pharmacotherapy has been recognized as a potential adjunct to other therapeutic approaches for treatment of language impairment due to brain damage (e.g., Albert, 1988; Berthier et al., 2011; Beversdorf, Narayanan, Hillier, & Hughes, 2007; de Boissezon et al., 2007; Klein & Albert, 2004; McNamara & Albert, 2004; Mimura, Albert, & McNamara, 1995; Small, 2000; Small, 1994; Small & Llano, 2009). Research efforts addressing the efficacy of such interventions have largely been guided by a clinical approach, with loose reference to neurobiology, whereby post-stroke neurochemical abnormalities are implicated in the breakdown of particular cognitive systems, and so can serve as targets of therapy. This approach is rooted in studies demonstrating how neurochemical manipulations of noradrenergic, dopaminergic, cholinergic, and glutamatergic mechanisms restore brain function in animal and human models (e.g., Small & Llano, 2009). However, in spite of encouraging results and the enthusiasm of its proponents, empirical findings describing beneficial effects of pharmacotherapy on language disorders remain limited, with mixed reports that call into question the efficacy of such treatments (e.g., Berthier et al., 2011; de Boissezon et al., 2007). It should come as no surprise, then, that “a language enhancement pill” has yet to find its way into common clinical practice in the treatment of language impairment. (For other factors limiting consistent use of drugs in aphasia treatment, see Berthier et al., 2011.)

What is it that makes results from pharmacotherapy studies of language impairment so elusive? Many of the observed inconsistencies are anchored in methodological problems (Berthier et al., 2011; de Boissezon et al., 2007; Small & Llano, 2009). These include issues such as sample selection (ignoring mixed etiologies as a source of variability in responsiveness to drug treatment), sample size (questioning the value of findings from case studies, small sample studies), time post onset (difficulty differentiating effects of spontaneous recovery from those of drug treatment), study design (bias in open label studies vs. randomized double-blind controlled trial, randomized double-blind placebo-controlled trial, randomized examiner-blind clinical trial), dosage of drugs administered (overdosing having the potential of leading to neurochemical dysregulation, worsening treatment outcomes), duration of intervention (interventions being insufficiently long to bring about change), and administration of drugs with concomitant language therapies (reduced efficacy of drugs as stand-alone treatments).

In this paper, we suggest an additional step in experimental design that may bring us closer to the goal of quantifying patient outcomes with increased precision. Specifically, we suggest that in the absence of theory-driven linguistic measures, it would be difficult to elucidate precise patterns of improvement in language performance resulting from pharmacotherapeutic intervention. Such a view has also been voiced by (Rapp, Caplan, Edwards, Visch-Brink, & Thompson, 2012), who pointed out the importance of task selection for interpretation of treatment effects in neuroimaging studies. We thus propose an integrative approach to the study of pharmacotherapy of language disorders: neurobiological considerations in selection of pharmacologic agents should be combined with theory-driven psycholinguistic considerations. This integrative approach might thereby allow researchers to pose confirmable hypotheses that could shed *new* light on the potential neurochemical systems correlated with specific linguistic deficits, leading to more precisely targeted interventions.

Our intention here is not to review once again the neurobiological promise that pharmacotherapy of aphasia may hold, but rather to highlight the importance of integrating psycholinguistic considerations into the design of such studies, which are essential for understanding the effects of such treatment. In what follows, then, we provide a brief review of the clinical approaches currently used in pharmacotherapy studies of aphasia, which have often been based on classical aphasiological phenomenology and, often, lack

psycholinguistic grounding. We then present ways in which psycholinguistic models can complement this approach, offering a rationale for task selection, and as a result, lead to a better understanding of treatment effects. We then follow with an example of how such an integrative approach can be implemented in studies targeting stress reduction as a means to augment language performance in people with aphasia (see also Cahana-Amitay et al., 2011). Our focus in this review will be primarily on post-stroke aphasia, although pharmacotherapy studies for language disorders are also being conducted in patients with other neurologic conditions, such as Parkinson's disease and primary progressive aphasia (see, for example, Angwin et al 2006; Reed et al 2004).

Pharmacotherapy of Aphasia: Current Perspectives

Pharmacotherapy is one of several biological approaches to treatment of aphasia used to stimulate post-stroke neural reorganization, on the premise that observed functional recovery directly reflects reparation of neural circuits mediating language and other cognitive functions (e.g., Lee & Hillis, 2008; Small & Llano, 2009).

Mechanisms of Aphasia Recovery: Rationale

Neurochemical interventions for aphasia are designed, among other reasons, to strengthen networks subserving language and language-related cognitive functions such as attention and memory (e.g., Berthier & Pulvermüller, 2011; Floel & Cohen, 2010). As previously pointed out, "... no single neurotransmitter is likely to underlie any complex cognitive process. Most such processes likely depend on the dynamic interplay of many neuromodulators, some perhaps not even identified as yet ..." (Albert, 2000, p. 157). Broadly speaking, recovery of these networks is associated with activation or reactivation of brain tissue in both the right and left hemispheres (e.g., Klein & Albert, 2004), which is accomplished via "reactive plasticity" (e.g., Nadeau & Wu, 2006). At the cellular level, different mechanisms are assumed to be involved in this process, e.g., neurogenesis, cell migration, axonal sprouting, dendritic elaboration, and changes in the excitability of existing synaptic connections. These mechanisms make unique temporal and spatial contributions to the restoration of activity in neural networks, both influenced by and influencing the local and wide-spread consequences of stroke-related factors, including lesion location/size (Heiss & Thiel, 2006; Lazar & Antonello, 2008); etiology (Klein & Albert, 2004), inhibitory and excitatory effects of various pharmacologic agents, etc., and therefore likely show distinct responses to pharmacotherapeutic interventions (Small & Llano, 2009).

Targeting Neurotransmitters

Neurochemical manipulations of neurotransmitter systems and their effects on language performance in aphasia have been explored in more than forty pharmacotherapy studies (see Berthier et al., 2011; Small & Llano, 2009). These studies examined the efficacy of drugs acting on noradrenergic, dopaminergic, cholinergic, and glutamatergic systems. Most efforts have been directed at exploring dopaminergic, noradrenergic and cholinergic effects, primarily on naming. The research focus in these studies was never driven by an explicit theory of "neurochemistry of language," but speculations were made about ways in which pharmacosystems might mediate certain aspects of lexical retrieval. Albert (2000), for example, proposed that dopaminergic pathways might support, in part, phonological output and articulation, whereas cholinergic pathways might contribute to lexical semantics. Beversdorf (2007) considered the role of reducing noradrenergic activity to suppress background neural activation, to increase the efficiency of lexical-semantic searches among people with aphasia with intact error monitoring (Beversdorf et al., 2007).

Dopaminergic and Noradrenergic Systems: Catecholamines

The most widely investigated class of drugs so far has been the catecholamines (e.g., Albert, 1988; Arciniegas, Frey, Anderson, Brousseau, & Harris, 2004; Berthier, 1999; Berthier, 2005; de Boissezon et al., 2007; McNeil et al., 1997; Raymer et al., 2001; Raymer, 2003; Seniów, Litwin, Litwin, Le niak, & Cżlonkowska, 2009; Walker-Batson et al., 1992; Walker-Batson et al., 2001; Whiting, Chenery, Chalk, & Copland, 2007; Leeman et al., 2011), such as Bromocriptine, Levodopa, Dextroamphetamine, and Amantadine, which are involved in neuromodulation of the dopaminergic and noradrenergic systems. Many of these pharmacotherapeutic interventions were carried out on the assumption that drugs targeting dopaminergic and noradrenergic deficiencies in damaged prefrontal, motor, and association cortices could improve language and speech motor functions associated with these areas, such as impaired lexical retrieval and verbal perseveration (e.g., Albert, 2000; McNamara & Albert, 2004). It was thought, for example, that stimulation of these neurotransmitter systems could benefit people with aphasia by augmenting the attentional systems necessary for activating different language output systems (Alexander, 2006; Crosson et al., 2005).

The expectation that language output would be positively affected by such neurochemical manipulation was supported both by evidence showing that the dopaminergic system operates in a lateralized fashion (McNamara & Albert, 2004), and by findings indicating that some catecholaminergic drugs specifically potentiate activity in frontal language-related networks if administered in conjunction with certain language tasks, such as verb generation (Sommer et al., 2006), or artificial vocabulary training (Breitenstein et al., 2004). Long-term retention of novel word learning has also been observed, following the administration of levodopa (Knecht et al., 2004). And, indeed, catecholamines have been shown primarily to affect disorders of *language output*, with the most efficacious results observed among people with non-fluent aphasia (Klein & Albert, 2004). Administration of dopamine agonists to such patients has been found to enhance speech initiation, reduce pauses and paraphasias in conversations, increase naming accuracy, improve repetition abilities, promote verbal (phonological) fluency, and shorten verbal latencies (Albert, 1988; Berthier, 1999; Berthier, 2005; Bragoni et al., 2000; Raymer et al., 2001; Raymer, 2003; Seniów et al., 2009).

However, these pharmacotherapeutic interventions have shown only varying degrees of success (e.g., Ashtary, Janghorbani, Chitsaz, Reisi, & Bahrami, 2006; Gupta & Mlcoch, 1992; Sabe, Salvarezza, García Cuerva, Leiguarda, & Starkstein, 1995) Leemann et al., 2011). The language gains reported were partial, especially among patients with moderate to severe impairment, in whom certain language problems (e.g., non-fluency) persisted even after treatment, showing limited to no long-term effects (Berthier et al., 2011). These disappointing results are attributable, in part, to one or more of the methodological issues listed in the Introduction. Nonetheless, better efficacy has been reported in studies in which drug delivery was coupled with evidence-based language treatments (e.g., constraint-induced language therapy), where neuroplasticity was enhanced in behaviorally-stimulated neural networks (see also Lee & Hillis, 2008; Shisler, Baylis, & Frank, 2000).

Cholinergic- and Glutamatergic-Based Drugs

Efforts have also been made to investigate the efficacy of drugs targeting cholinergic and glutamatergic neurotransmitter systems for aphasia recovery, such as Ameridin, Bifemelane, Aniracetam, Galantamine, Piracetam, Donepezil, and Memantine, inspired, in part, by pharmacotherapy studies in Alzheimer's disease and vascular dementia (Berthier et al., 2011; Klein & Albert, 2004; Small & Llano, 2009). Evidence of increased left-lateralized cholinergic activity in the brain, especially in the temporal lobe (Albert, 2000), has led to the conjecture that a deficiency in this neurotransmitter system might result in adverse effects for language abilities dependent on verbal memory (e.g., Klein & Albert, 2004; Mimura et

al., 1995). Patterns of impaired naming and reduced verbal fluency among healthy young women following administration of a drug blocking cholinergic activity (Aarsland, Larsen, Reinvang, & Aasland, 1994) lend support to this idea. Additional support comes from studies reporting perseverative and paraphasic errors among aphasic patients with cholinergic deficiencies (Berthier, Hinojosa, & Moreno-Torre, 2004; Corbett, Jefferies, & Lambon Ralph, 2008; Gotts, della Rocchetta, & Cipolotti, 2002; McNamara & Albert, 2004).

The mechanisms by which cholinergic- and glutamatergic-based interventions could lead to improved language functions, however, remain unclear. Berthier and colleagues, for example, have suggested that stimulating interrupted cholinergic pathways in damaged basal forebrain, peri-sylvian, brainstem, and thalamic areas, can enable encoding of linguistic information and filtering of task-irrelevant noise via top-down increases in sensory input (Berthier & Pulvermüller, 2011; Berthier et al., 2011). This idea is based, in part, on the observation that cholinergic activity is involved in long-term neural potentiation required for processes of attention and learning/memory (Sarter, Hasselmo, Bruno, & Givens, 2005). Stimulation of glutamatergic activity in the brain, in contrast, has been argued to increase the efficiency with which spared neural networks operate, augmenting recovery, especially when coupled with behavioral programs, such as constraint-induced language therapy (Berthier et al., 2009; Pulvermüller et al., 2001).

In several studies, cholinergic or glutamatergic-based interventions have, indeed, been found to improve performance on naming and comprehension tasks among aphasic patients with posterior lesions and patients with fluent aphasia (e.g., Berthier et al., 2006; Berthier, Hinojosa, Martín, & Fernández, 2003; Berthier et al., 2009; Chen et al., 2010; Huber, Willmes, Poeck, Van Vleymen, & Deberdt, 1997; Kessler, Thiel, Karbe, & Heiss, 2000; Lurija, 1970; Pulvermüller et al., 2001; Tanaka & Albert, 2001; Tanaka, Miyazaki, & Albert, 1997). Language improvements in these studies cover multiple domains, including, for example, improved articulation, increased amount of spontaneous speech, greater naming accuracy, faster latencies, improved repetition, better semantic and phonemic discrimination, and enhanced word- and sentence-picture matching abilities (Berthier et al., 2011). In some cases, such improvements have also been associated with increased blood flow in frontotemporal regions (Kessler et al., 2000). Because the most consistent benefits have been observed in word retrieval abilities, and because anomia continues to constitute the hallmark of aphasic language disorder in all patients with long-term aphasia (see Lazar & Antonello, 2008), drugs, such as donepezil have been argued to be particularly promising for aphasia treatment in its chronic stages (Berthier et al., 2011). However, at this point, claims about the efficacy of these interventions are tentative, as consistent findings of long-term benefits in cases of large lesions have yet to be reported (e.g., Güngör, Terzi, & Onar, 2011).

Efficacy of Aphasia Pharmacotherapy: Quantifying Effects

Among the obstacles to demonstrating efficacy of pharmacological intervention for aphasia is quantification of patients' responses to treatment in a statistically valid and reliable manner. No less important is the personal response of the patient. In pharmacotherapy studies of aphasia (or any therapy study, for that matter) statistical improvement on a standardized test must be coupled with a clinically meaningful response. The patient should get better, and know it. In many of the review papers on this topic (e.g., Berthier et al., 2011; de Boissezon et al., 2007; Small & Llano, 2009), detailed discussions of methodological and measurement problems are highlighted, with some suggestions on how shortcomings might be addressed. Small & Llano, 2009, for example, stated: "In our view, the optimum study design to establish that a pharmacological agent promotes brain reorganization to enhance

language processing would be a double-blind, placebo-controlled, adequately-powered, parallel group study that contains at least one outcome measure that is assessed after drug washout to ensure that any benefit observed is not only due to temporary enhancement of arousal” (p.445). Berthier et al., 2011 have even conducted a reanalysis of previously collected data (Berthier et al., 2006; Berthier et al., 2003) to address the issue of inter-patient variability often observed in biological intervention studies (Berthier et al., 2009; Cherney, Erickson, & Small, 2010). They quantified the proportion of participants who responded to the administration of donepezil, a cholinergic-based drug, using changes in Aphasia Quotient scores of the Western Aphasia Battery (Kertesz, Sheppard, & MacKenzie, 1982), compared to baseline performance, as a measure of reduction in aphasia severity.

However, in spite of this deep understanding of the caveats associated with the experimental design of aphasia pharmacotherapy studies (e.g., Berthier et al., 2011), investigations continue to produce inconsistent results. We believe that this picture is partially determined by the inadequacy of the linguistic measures used in these studies to assess language improvement in treated patients. Selection of relevant diagnostic language tasks in any treatment study should ideally be driven by a theory of language that outlines a certain degree of linguistic specificity, in order to predict where linguistic dysfunction might occur and what kinds of errors can be expected (see Rapp, Caplan, Edwards, Visch-Brink, & Thompson, 2012, for an analogous argument). A quick look at the linguistic measures used in many of the published aphasia pharmacotherapy studies indicates that their choice has rarely been motivated by systematic psycholinguistic considerations. Table 1 lists linguistic tasks which have been used to assess treatment-based language change in different aphasia pharmacotherapy studies to date.

These outcome measures usually consist of scores on standardized tests, such as Boston Naming Test (Kaplan, 1983), Action Naming Test (Obler & Albert, 1979), and Verbal Fluency Test (Benton & Hamsher, 1976), which are clinically driven. The underlying assumption in these studies being that impairments in language fluency, comprehension, repetition, reading, and writing will improve post-treatment based on aphasia classification and severity. These clinical distinctions might lack sufficient granularity to capture fine-grained language changes following treatment. We, thus, argue that in the absence of a clear psycholinguistic theoretical basis for task selection, the interpretability of pharmacotherapeutic effects on people with aphasia becomes difficult. We suggest using psycholinguistic models in conjunction with neurobiological approaches to aphasia recovery, to establish a clear rationale for the experimental design of aphasia pharmacotherapy studies, especially for the linguistic tasks chosen to measure treatment outcomes.

Psycholinguistics of Aphasia Pharmacotherapy: A New Frontier

How might one approach a pharmacotherapy study of aphasia from a psycholinguistic perspective? Rapp et al. (2012) considered a similar question in relation to aphasia treatment studies using neuroimaging techniques, which also face a comparable challenge of reconciling mixed, incongruent results. They identified crucial methodological prerequisites, which, if followed, would likely improve the experimental design of such studies, increasing interpretability of results. In what follows, then, we follow Rapp et al.’s (2012) rationale, in proposing how psycholinguistic rigor can be applied in aphasia pharmacotherapy studies.

Psycholinguistic Considerations

A first step in identifying treatment-based language changes resulting from pharmacotherapy in people with aphasia would be the creation of a language profile of pre-

treatment baseline performance, based on a given psycholinguistic theoretical framework. Such a profile would involve characterizing pre-intervention impaired and spared functions, which could then be compared to post-intervention performance and allow for identification of treatment-based effects. To isolate these treatment effects, the tasks selected should be designed to detect dissociations in the patterns of errors produced by study participants.

As Rapp et al.(2012) point out, when studying naming deficits, for example, a reasonable psycholinguistic framework could include the assumption that spoken word production engages multiple processes, distinguishing semantic, lexical, phonemic, and motor production levels (e.g., Rapp & Goldrick, 2006). Thus, to identify whether or not a drug “improves” naming, the experimenters would first have to rule out impaired vision and hearing, semantic problems (e.g., by testing auditory comprehension), and motor problems (e.g., by testing repetition abilities). Then they would need to be able to help determine which underlying psycholinguistic mechanism affects the naming errors produced—semantic and/or phonemic (e.g., by examining paraphasias and determining which cues are more helpful for increasing naming accuracy).

Rapp et al. (2012) caution that in order to reliably isolate treatment effects on language performance, pre- and post-intervention evaluations should also be accompanied by a comprehensive assessment of language-related cognitive domains, such as attention, working memory, and executive functions. In principle, more precise characterization of specific effects on language performance can be obtained if comparisons between experimental vs. control tasks are made (e.g., Caplan, 2009). However, from a neurochemical perspective, it is likely that pharmacological manipulation of a given neurotransmitter system will affect linguistic and, to some extent, other related cognitive processes, dependent on the functionality of its pathways. Thus, a psycholinguistic model which postulates interdependencies between linguistic operations and specific cognitive functions, such as attention, inhibition, or set shifting, will likely best predict patterns of deficits resulting from neural changes. Support for this idea comes from the growing literature describing the co-morbidity of different cognitive deficits and language impairment which can be observed among people with aphasia (e.g., Martin & Reilly, 2012; Kurland, 2011). Studies of language changes among healthy older adults also points in this direction, as executive functions, such as working memory and inhibitory control, have been associated with both preservation and decline of different language functions, such as sentence processing (e.g., Goral et al., 2011).

Combining Psycholinguistics and Neurobiology: The Case of Beta-Adrenergic Blocking Agents

We offer here an example of the principal thesis being proposed in this paper: an integrative approach to aphasia pharmacotherapy could be used to investigate the efficacy of beta adrenergic drugs for the augmentation of language performance in people with aphasia. Preliminary evidence suggests that administration of a beta blocking agent, such as propranolol, positively affects language performance in people with aphasia, improving, for example, their naming abilities(Beversdorf et al., 2007; Tanaka, Albert, Fujita, Nonaka, & Oka, 2007; Tanaka et al., 2010). Because such agents block the receptors for the physical effects involved in the natural “fight or flight” response (e.g., increased heart rate), inhibiting negative feelings of impending danger (e.g., anxiety), some researchers have speculated that beta blockers act to decrease autonomic nervous system (ANS) physiological responses (e.g., reduce heart rate) to improve language performance, in ways comparable to the amelioration of the phenomenon of “performance anxiety” in otherwise healthy individuals (Tanaka et al., 2010). Beta-adrenergic enhancement of naming has also been explained in terms of modulation of signal-to-noise ratio in the cortex (Hasselmo, Linster, Patil, Ma, & Cekic, 1997; Heilman, Nadeau, & Beversdorf, 2003), resulting in increased

efficiency of information processing. Although these different theoretical accounts can potentially be teased apart by studies distinguishing peripheral and central autonomic components in persons with and without aphasia (Cahana-Amitay et al., 2011), they fail to make specific predictions as to the types of errors the pharmacological intervention might alleviate.

More explicit predictions about the consequences of ANS dysregulation can be made, for example, using Cahana-Amitay et al.'s (2011) framework of “linguistic anxiety” in aphasia, which postulates that altered ANS activity, as measured by stress-induced physiologic responses (e.g., changes in heart rate), can adversely affect language performance in aphasia, especially on tasks with heavy attention demands. In their view, people with aphasia who experience language use as a stressor (e.g., when speaking in front of strangers, when attempting to follow a conversation in noisy conditions) also demonstrate changes in physiologic stress reactivity, which might further impair their performance on the language task. This physiologic change is then assumed to lead to a resource allocation imbalance, whereby attention resources that would otherwise be allocated to task performance, are directed towards suppressing hyper-concerns about the challenges of the language task, continually reinforced by aroused physiologic stress responses. The most adverse effects on performance would be observed in situations where the processing of linguistic information in the presence of competing stimuli is required, as the suppression of worry would be competing for the same attention resources required for processing task-relevant information.

Given this theoretical framework, *the benefits of using beta-blocking agents to improve language performance among people with aphasia can be evaluated anew by examining changes in performance of language tasks involving inhibition of non-target competitors, as a result of the pharmacological intervention.* To identify pre- and post-treatment effects, it would be necessary first to assess the presence of physiologic stress reactivity, using physiologic biomarkers of ANS activity, such as heart rate variability, galvanic skin responses, or blood pressure. Then, an evaluation of attention abilities would be required, to rule out a general attention dysfunction (e.g., sustained vigilance, working memory) that might interfere with language performance (for types of attention tasks that can be used to assess people with aphasia (see Connor & Fucetola, 2011). Finally, assessment of performance on language tasks with and without competing stimuli would have to be done, to determine whether they are differentially affected by treatment. The determination of what constitutes a “competing target” depends entirely on the research interests of the investigator. Competition can occur at any linguistic level—semantic, phonological, sentential, and discursive—and affect many language functions, including language production, auditory comprehension, and reading comprehension (e.g., Connor & Fucetola, 2011; Kurland, 2011).

Regardless of the source of linguistic competition, the research hypothesis would be that beta adrenergic manipulation would ameliorate performance of language tasks involving competing stimuli by targeting ANS biomarkers and freeing up attention resources taxed by the increased stress. Note that these treatment effects are expected to be more modest in people with a general attention dysfunction. In such people, attention problems are likely to be mediated by additional neurochemical mechanisms independent of those associated with increased stress, and so are less likely to improve in response to this particular pharmacological intervention. These people might respond better to pharmacotherapies directly targeting attention deficits (e.g., dopamine agonists). Speculations about such treatment effects cannot be made using scores on standardized language tasks, as those tests often lack the diagnostic sensitivity to differences in attention processing demands and might therefore fail to reflect distinct treatment effects.

Asking the Right Questions

The extent to which psycholinguistics can inform aphasia pharmacotherapy studies is constrained by the degree to which language assessments that take psycholinguistic factors into account are utilized in aphasia therapy. Psycholinguistic models have been steadily working their way into aphasia treatment programs. Some treatments of naming impairment, for instance, have been based on a psycholinguistic model of semantic feature complexity that specifies exemplar typicality (e.g., Kiran & Johnson, 2008; Kiran & Thompson, 2003). Or, treatment of certain sentential deficits have been designed to reflect a language model differentiating sentence types by level of syntactic complexity (e.g., Thompson, Den Ouden, Bonakdarpour, Garibaldi, & Parrish, 2010; Thompson, Shapiro, Kiran, & Sobecks, 2003; Thompson & Shapiro, 2007). These attempts bode well for the incorporation of psycholinguistic models into aphasia pharmacotherapy studies, promising to increase the resolution with which we can identify functional changes resulting from neurochemical manipulation of specific neurotransmitter systems.

This review paper has a specific, and limited, goal: to highlight psycholinguistic gaps in the current aphasia pharmacotherapy literature and to emphasize the importance of incorporating contemporary psycholinguistic knowledge into clinical research studies of aphasia pharmacotherapy. We do not wish to suggest that there should be a “one-size-fits-all” approach to the study of drug effects on language performance among people with aphasia. Clearly, single-case studies, small case series, controlled proof-of-principle experiments, and controlled clinical trials have different goals and, therefore, distinct methodologies, each with its own strengths and shortcomings. Smaller-scale studies might, perhaps, lend themselves more easily to the exploration of fine-grained theoretically-motivated dependent outcomes measuring language impairment.

If we take the examination of the effects of beta-adrenergic blocking agents on word retrieval as an example, one could imagine administration of an extensive language battery to up to twelve individuals, designed to measure baseline, mid-, and post-intervention performance, using accuracy scores and/or reaction times on tasks that vary in their processing demands. These tasks might include lexical decision tests with or without a competing distractor, cloze-completion tasks involving sentences that vary in syntactic complexity, or noun and verb retrieval rates in discourse tasks with thematically-linked content but differing discourse demands (e.g., examining nouns/verbs per minute in a stroke narrative vs. an expository opinion about treatment of stroke in the healthcare system). Results from such small-scale studies are likely to help determine which language measures most compellingly reflect treatment-induced changes in performance, which could then be incorporated into a larger-scale study. We recognize the many difficulties inherent in aphasia treatment studies, pharmacotherapeutic or other, but propose this new direction, nonetheless, as a challenge worth undertaking, as it may enable the detection of the beneficial effects of treatment not previously considered, that may have both theoretical and clinically meaningful consequences.

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Table 1

Pre- and Post-Treatment Linguistic Measures Used in Aphasia Pharmacotherapy Studies

Author, Year	Drug	n	Etiology	Aphasia Type & Severity (Pre-treatment)	Concurrent Treatment	Linguistic Outcome Measures (Pre- & Post-Treatment)	Results
Albert et al. (1988)	bromocriptine	1	CVA (hemorrhage)	Moderate TCMA; BDAE: 3.5	None specified	BDAE subtests, Cookie Theft picture description, latency of response, pauses	Improvement: reduced latency of response, decreased paraphasias, increased naming ability; language returned to baseline after treatment stopped
MacLennan et al. (1991)	bromocriptine	1	CVA (ischemic)	TCMA	None specified	Captain's Log Stimulus Visual Reaction Time, Token Test, BNT, verbal fluency, BDAE, other speech samples, mood & ability to communicate questionnaire	No significant effect
Gupta & Milcoch (1992)	bromocriptine	2	CVA	Nonfluent aphasia	None specified	BDAE, BNT, Mean length of utterance (MLU)	Improvements in verbal fluency and naming; increased MLU
Sabe et al. (1992)	bromocriptine	7	CVA	Moderate to severe nonfluent aphasia; 4 TCMA, 2 Broca's, 1 Global	None specified	WAB figure description; lexical index, grammatical index, verbal fluency, significant words, pauses (>3s)	No improvements for patients with severe aphasia; improvements in lexical index and fluency and decreased number of pauses for the mild patients; these improvements declined after reducing/discontinuing the medication.
Gupta et al. (1995)	bromocriptine	20	Brain injury, unspecified	Nonfluent aphasia; TCMA, Broca's, Mixed	None specified	WAB, BNT, RCPM	No significant effect
Ozeren et al. (1995)	bromocriptine	4	CVA	Nonfluent aphasia; 2 Broca's, 1 Global, 1 TCMA	None specified	"Aphasia tests"	No effect
Sabe et al. (1995)	bromocriptine	7	5 CVA (ischemic), 2 TBI	Moderate nonfluent aphasia; 2 Broca's, 3 TCMA, 2 Anomic	None specified	WAB, BDAE figure description, BNT, verbal fluency (FAS)	No significant effect
Gold et al. (2000)	bromocriptine	4	CVA	Nonfluent Aphasia; 2 Broca's, 2 TCMA; AQ Range: 41–84.8	None specified	Gold, Rosen & Silliman object-naming task; reaction times, storage & retrieval quotients	Improvements in word retrieval quotient; declines in time latency; no effect on word storage quotient
Bragoni et al. (2000)	bromocriptine	11	CVA	Nonfluent; Broca's, Global; Severity range: mild to severe	Speech therapy, not detailed	Standardized Italian language test; Token test, FAS, set test, cookie theft, sentence generation, visual naming, verbal latency	Improvement observed in dictation, reading comprehension, and verbal latency
Raymer et al. (2001)	bromocriptine	1	CVA	Crossed nonfluent aphasia; TCMA; WAB Aphasia Quotient: 79.8	None specified	WAB, BNT, verbal fluency (FAS), Florida Apraxia Screening Test-Revised, procedural discourse	Improvement in verbal fluency; no improvement in gesture or emotional prosody
Reed et al. (2004)	bromocriptine	6	Progressive	PPA	None specified	Discourse analysis; MLU, proportion of grammatical sentences, noun-verb ratio, open-class/closed-class	No significant effect
Ashtary et al. (2006)	bromocriptine	38	CVA	Nonfluent aphasia	None specified	Standardized Persian language test	No significant effect

Author, Year	Drug	n	Etiology	Aphasia Type & Severity (Pre-treatment)	Concurrent Treatment	Linguistic Outcome Measures (Pre- & Post-Treatment)	Results
Seniow et al. (2009)	levodopa	39	CVA	All levels of aphasia severity range (0–5)	SLT: 45 minutes, 5 days/week for 3 weeks	BDAE	Language improvements in verbal fluency and repetition, particularly among patients with anterior lesions
Leeman et al. (2011)	levodopa	12	CVA, TBI	Wernicke's, Broca's, Conduction, Anomia	SLT: standard clinical treatment (4–5 hrs/week); additional daily Computerized Aphasia Therapy (CAT)	Battery of naming tasks	No significant effect
Walker-Batson et al. (1991)	d-amphetamine	1	CVA	Broca-type aphasia; AQ: 32.5	SLT: 75 minutes every 4th day for 6 weeks (12.5 hours); treatment focused on verbal performance	PICA, BDAE	PICA improvement greater than PICA recovery prediction
McNeil et al. (1995)	d-amphetamine	1	Progressive	PPA	SLT: Individual sessions 3 hrs/week for 5 months; focused on cuing hierarchy for producing antonym and synonym adjectives	PICA, Revised Token Test, RCPM, RAN; standardized narrative discourse	Treatment effective for antonym and synonym adjectives; language declines in standardized domains; differential effects of behavioral treatment and pharmacological + behavioral intervention were not observed
McNeil et al. (1997)	d-amphetamine	2	CVA	Mild to moderate aphasia and co-occurring apraxia of speech	Lexical-semantic activation inhibition therapy (L-SAIT) present in one condition, absent in one condition	RAN; connected speech measures	No effects in absence of L-SAIT; positive treatment effects attributed to L-SAIT
Walker-Batson et al. (2001)	d-amphetamine	21	Non-hemorrhagic infarction	Aphasia, PICA score between 10–70	SLT: 1-hr individual session 3–4 days/week; protocol individualized as needed for each patient's specific needs	PICA	D-amphetamine paired with speech/ language treatment accelerated rate of recovery in subacute stage
Whiting et al. (2007)	d-amphetamine	2	Chronic aphasia	Chronic aphasia	SLT: 2, 4-week blocks of naming therapy, 2–3 sessions/week	Confrontation naming task	Greater therapy progress with addition of d-amphetamine rather than placebo; improvement difference significant for only one individual
Darley et al. (1977)	methyphenidate vs. chlordiazepoxide	14	TBI, CVA		None specified	PICA, Word fluency	No effect of either drug
Barrett &Eslinger (2007)	amantadine	4	CVA, CVA + aneurysm surgery, brain tumor resection	Nonfluent; TCMA	SLT: 1 hr, 5 days/week	Controlled Oral Word Association Test	Improvements in word generation
Kertesz et al. (2008)	galantamine	36	Progressive	PPA	None specified	Frontal Behavior Inventory, WAB, Clinical Global Impression of Severity, Clinical Global Impression of Improvement	No significant differences in behavior or language; language scores for galantamine group remained stable while placebo group scores deteriorated
Hong et al. (2012)	galantamine	45	CVA	Chronic aphasia	None specified	Four domains of WAB-AQ; MMSE	Significant increase in AQ scores for galantamine group but not control group
Tanaka et al. (1997)	bifemelane	4	CVA	Fluent aphasia	SLT: conventional aphasia therapy 3 times/week	Standard Language Test for Aphasia	Improvements in comprehension and naming for treatment group; no change in language for non-treatment group

Author, Year	Drug	n	Etiology	Aphasia Type & Severity (Pre-treatment)	Concurrent Treatment	Linguistic Outcome Measures (Pre- & Post-Treatment)	Results
Tanaka & Albert (2001)	aniracetam	8	CVA	Wernicke's aphasia, mild and severe	None specified	BNT, ANT, Word generation test for categories, tests of perseveration; tests of verbal memory	Improvement on BNT, ANT, word generation and decreased perseveration for non-severe patients
Pashek& Bachman (2003)	donepezil	1	CVA	Broca's aphasia with moderately severe verbal apraxia	None specified	BNT, ANT, BDAE, Token test, attention tests	Consistent improvement in language, cognition, and motor speech; improvements maintained at follow-up testing
Berthier et al. (2006)	donepezil	26	CVA	Broca's, anomic, conduction, and Wernicke's aphasia	SLT; 2 hrs/week; Syndrome-specific standard approach	WAB, CAL, PALPA, Stroke Aphasic Depression Questionnaire	Improvement in aphasia severity with donepezil relative to placebo
Chen et al. (2010)	donepezpil	60	CVA	Acute aphasia	None specified	WAB	Significantly greater improvement in donepezil group than control group
Berthier et al. (2009)	memantine	27	CVA (ischemic, hemorrhagic)	Chronic aphasia	CIAT; 30 hours within 2 weeks for each patient	WAB, CAL	Greater improvement with CIAT and memantine treatment than CIAT alone; beneficial effects persisted long-term
Johnson et al. (2010)	memantine	18	Progressive	Mild to moderate PPA	None specified	WAB	No significant effect; smaller degree of decline on WAB aphasia quotient in drug group
Huber et al. (1997)	piracetam	66	CVA, TBI, brain surgery unrelated to malignant tumor	Moderate to severe aphasia	Speech Therapy: 10 (5 individual, 5 group) sessions; 60-min sessions/week for 6 weeks	AAT	Greater significance for piracetam than placebo for "written language" and "profile level"
Orgogozo (1999)	piracetam	373	CVA (ischemic)		SLT, not detailed	Frenchay Aphasia Screening Test	Greater percentage with aphasia recovery in piracetam group compared to placebo group
Kessler et al. (2000)	piracetam	24	CVA (ischemic)	Mild to moderate aphasia	SLT; 5 60-min sessions/week for 6 weeks	AAT, FAS, Corsi's block span test, tests of apraxia, RCPM, Benton Test	AAT: piracetam increased 7 sub-scores
Gungor et al. (2011)	piracetam	30	CVA (ischemic)	moderate to severe aphasia	None specified	NIHSS, Gulhane Aphasia Test	No clear benefit
Tanaka et al. (2006)	propanolol	10		Broca's and Wernicke's aphasia	None specified	BNT, verbal fluency (FAS, vegetables)	Short-term beneficial effect on naming
Beversdorf et al. (2007)	propanolol	4	CVA (ischemic)	Broca's Aphasia with anomia	None specified	BNT	Greater improvement in naming with propanolol than placebo
Tanaka et al. (2010)	propanolol	11		Mild to moderate Broca's, Wernicke's, and amnesic aphasia	None specified	BNT, ANT, verbal fluency (category), auditory comp, BDAE Cookie Theft	Significant improvement for all subjects on BNT, ANT, verbal fluency, and auditory comp tests; one month after discontinuation of propanolol scores returned to baseline
Tanaka et al. (2004)	fluvoxamine vs. nilvadipine	10	CVA (ischemic, hemorrhagic)	Fluent aphasia; Wernicke's/jargon aphasia	None specified	WAB (Japanese version), BNT, ANT, word generation, BDAE, Token Test	Improvements in naming and mood, decreased perseveration with fluvoxamine (SSRI) for non-severe patients
Cohen et al. (2004)	zolpidem	1	CVA	Severe Broca's aphasia	None specified	Non standardized language exam	20 min after each administration, striking improvement of speech fluency, w/accurate and meaningful

Author, Year	Drug	n	Etiology	Aphasia Type & Severity (Pre-treatment)	Concurrent Treatment	Linguistic Outcome Measures (Pre- & Post-Treatment)	Results
Laska et al. (2005)	moclobemide	90	CVA		None specified	Grunntest for afasi, Amsterdam-Nijmegen-everyday-language-test	words, repetition of words, pseudo-words and short sentences No significance
Tsikunov & Belokoskova (2007)	vasopressin	26	CVA (ischemic)	Acousto-agnostic and acousto-amnesic aphasia	None specified	Battery of speech-language subtests (e.g. naming, comprehension, repetition, spontaneous speech, verbal fluency, reading, etc)	Differential improvement in domains of speech/language depending on aphasia type
Jianu et al. (2010)	cerebrolysin	156	CVA (ischemic)	Broca's aphasia	Standard therapy within 72 hours from stroke onset	Romanian WAB, NIHSS	Improvement in AQ, spontaneous speech, naming, and repetition with adjuvant cerebrolysin treatment

AQ, Aphasia Quotient; **WAB**, Western Aphasia Battery; **PICA**, Porch Index of Communicative Ability; **BNT**, Boston Naming Test; **BDAE**, Boston Diagnostic Aphasia Examination; **ANT**, Action Naming Test; **PALPA**, Psycholinguistic Assessments of Language Processing in Aphasia; **RCPM**, Raven's Colored Progressive Matrices; **CAL**, Communicative Activity Log; **AAT**, Aachen Aphasia Test; **NIHSS**, National Institute of Health Stroke Scale; **RAN**, Rapid Automatized Naming; **CVA**, cerebrovascular accident; **TBI**, traumatic brain injury; **TCMA**, transcortical motor aphasia; **PPA**, primary progressive aphasia; **SLT**, speech-language therapy; **CIAT**, constraint-induced aphasia therapy; **MMSE**, Mini Mental State Exam; **SSRI**, selective serotonin reuptake inhibitor