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Dexamphetamine boosts naming treatment effects in chronic aphasia

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Abstract

To date, minimal research has investigated the effect of combining dexamphetamine with standard naming therapy after stroke. The present study used a double-blind, placebo-controlled, multiple baseline, crossover design with two individuals in the chronic stage of stroke recovery. Each individual attended two 4-week blocks of naming therapy (two to three treatment sessions per week). Dexamphetamine (10 mg) was administered at the start of each session during one therapy block, while a placebo was administered during the other therapy block. Therapy progress on treated and untreated items was assessed by a confrontation naming task during and after each therapy block. Both individuals showed greater progress in therapy and maintenance of therapy gains when behavioral treatment was combined with dexamphetamine rather than placebo, although this gain was only statistically significant in one individual. There was no significant improvement on a control task (nonword reading) in either individual. The results provide preliminary evidence that dexamphetamine paired with combined semantic and phonological therapy may be beneficial for the treatment of naming disorders in chronic aphasia. (*JINS*, 2007, *13*, 972–979.)

Keywords: Pharmacotherapy, Amphetamine, Stroke, Anomia, Naming therapy, Aphasia

INTRODUCTION

Previous research has found that dexamphetamine can improve general speech/language recovery in the acute recovery stage after stroke in a nonblinded single case study (Walker-Batson et al., 1990) and in a nonblinded case series study with six participants (Walker-Batson et al., 1992). However, the significance of these results is difficult to gauge, given the open label (nonblinded) nature of the studies. Nonetheless, a more recent double-blind, placebo-controlled study by Walker-Batson and colleagues (2001) also found that dexamphetamine improved general acute-stage speech/language recovery compared with a placebo.

To date, few studies have specifically investigated the effects of dexamphetamine on word retrieval therapy. McNeil et al. (1997) found that dexamphetamine did not improve naming beyond the level achieved with behavioral therapy (therapy involved synonym and antonym generation) in an individual with chronic aphasia poststroke. It is important to note that the participant was 3 years poststroke. The time frame during which dexamphetamine may assist functional recovery poststroke remains unknown (de Boissezon et al., 2007; Knecht et al., 2001; Nadeau & Wu, 2006; Shisler et al., 2000; Walker-Batson et al., 2004), however, it has been argued that it may be more effective in the acute recovery stage (de Boissezon et al., 2007; Walker-Batson et al., 2004), thus the participant may have been at a recovery stage where dexamphetamine was of little benefit. The finding by McNeil et al. (1997) that naming improved only when the participant received behavioral therapy, but not the drug alone, is consistent with data suggesting that dexamphetamine is most effective when administered in conjunction with behavioral therapy designed specifically to target the neurological impairment (Crisostomo et al., 1988; Long & Young, 2003; Martinsson & Eksborg, 2004; Nadeau & Wu, 2006; Nudo et al., 2001; Walker-Batson et al., 1995). Of interest, research with healthy adults has also found that dexamphetamine paired with task-specific training can significantly facilitate normal behavioral learning mechanisms (e.g., Breitenstein et al., 2004; Nadeau & Wu, 2006; Soetens et al., 1995; Whiting et al., 2007a,b).

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In summary, evidence suggests that pharmacological agents may be beneficial during aphasia therapy. However, exactly which pharmacological agents and which aphasia symptoms and treatment tasks are most responsive to pharmacological intervention remains unknown. The present study aimed to investigate the effects of combining dexamphetamine with a current behavioral naming therapy approach (e.g., Drew & Thompson, 1999; Nettleton & Lesser, 1991). The present study was more constrained than previous studies (e.g., Walker-Batson et al., 1990, 1992, 2001) in that it was limited to individuals with anomic aphasia, therapy tasks were limited to noun retrieval only, a set amount of therapy was provided, and item-specific outcome measures were used to determine the specificity of treatment effects. In this study, we tested the adjuvant effects of dexamphetamine in chronic stroke patients, with the effects likely to be mediated through the potentiation of normal learning mechanisms. In contrast, prior studies (Walker-Batson et al., 1990, 1992, 2001) tested the potential adjuvant effects of dexamphetamine in individuals with subacute stroke, in which the effects of dexamphetamine were likely mediated through the potentiation of spontaneous reactive neuroplasticity. The analysis of our results was facilitated by the fact that, in contrast to participants in subacute studies, our participants were no longer experiencing spontaneous recovery.

Table 1. Participant BNT and PALPA assessment scores during the pretreatment sessions

Assessment	P1	P2
BNT	30/60*	25/60*
Correct responses with phonemic cueing	3/30	19/34
PALPA Auditory synonym judgments		
High imageability	24/30*	27/30*
Low imageability	15/30*	23/30*
PALPA auditory lexical decision		
High imageability High frequency	20/20	20/20
High imageability Low frequency	20/20	19/20*
Low imageability High frequency	18/20*	20/20
Low imageability Low frequency	16/20*	19/20[a]
PALPA Nonword repetition[b]		
1 syllable	3/10	9/10
2 syllable	7/10	8/10
3 syllable	9/10	9/10
PALPA Nonword reading		
3 letter	6/6	5/6[a]
4 letter	6/6	4/6*
5 letter	6/6	4/6*
6 letter	5/6	2/6*

Note. BNT = Boston Naming Test (Kaplan et al., 1983); PALPA, Psycholinguistic Assessment of Language Processing in Aphasia (Kay et al., 1992).
[a]Borderline between intact and impaired functioning;
[b]No norms available. Norms were obtained from individual test manuals referenced above.
*Below the cutoff for intact functioning.

METHODS

Participants

Two right-handed, monolingual English speaking individuals with aphasia (P1 and P2) were recruited to participate in the study. Inclusion criteria included (a) a single stroke at least 6 months previously, and (b) vision (with or without corrective devices), hearing, and body weight within normal limits. Exclusion criteria included (a) any psychiatric, other neurological, or degenerative disorders/diseases; (b) obstructive sleep apnea; (c) a history of substance abuse; (d) significant motor speech disorders; (e) currently receiving α-adrenergic antagonist or agonist medication, antidepressants, or tranquillizers; or (f) regular cigarette smoking.

To determine the locus of each participant's naming difficulties, participants completed the Boston Naming Test (BNT; Kaplan et al., 1983), the Comprehensive Aphasia Test (CAT; Swinburn et al., 2004), and selected subtests from the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA; Kay et al., 1992; see Tables 1 and 2). The BNT was administered to estimate the severity of each participant's naming difficulties and to gauge the effectiveness of phonemic cues. The CAT was administered to provide an overall profile of the functioning of the different components of the single word processing model (e.g., Patterson & Shewell, 1987) for each participant. The PALPA auditory synonym judgment task, auditory lexical decision, nonword repetition, and nonword reading tasks were administered to evaluate the functioning of each participant's semantic system, phonological input lexicon, auditory-to-phonological conversion route, and orthographic-to-phonological conversion route.

P1 was a 76-year-old, right-handed, retired female farmer with 15 years of education. P1 was admitted to hospital in May 2001 with an acute right basal ganglia infarct in the branches of the right middle cerebral artery. As P1 was right-handed and had experienced a right-sided stroke, the presence of a crossed aphasia was suggested (Raymer et al., 2001). Upon entering the present study, P1's language production was fluent. P1's errors on the BNT at this time consisted predominantly of no responses and semantic errors, with some circumlocutory responses (see Table 1). Phonemic cues were of little use, with only 3/30 phonemic cues being effective. The locus of P1's naming difficulties was analyzed in terms of a single word processing model (Patterson & Shewell, 1987). As language assessments found that (a) P1's naming difficulties were susceptible to imageability, (b) her semantic memory and comprehension of words was compromised, and (c) semantic distractors were the predominant error type in spoken and written naming, impairment at the conceptual–semantic level was probable (Cole-Virtue & Nickels, 2004; Howard & Gatehouse, 2006; Nickels, 2001; Whitworth et al., 2005). Frequency effects on an auditory lexical decision task suggested that there

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Table 2. Participant CAT assessment scores during the pretreatment sessions

Subtest	P1	P2
Cognitive screen		
Line bisection	0	−1.5
Semantic memory	7/10*	10/10
Word fluency	8*	8*
Recognition memory	6/10*	10/10
Gesture object use	11/12	12/12
Arithmetic	4/6	4/6
Language comprehension		
Spoken words	28/30	30/30
Spoken sentences	26/32*	29/32
Spoken paragraphs	3/4	3/4
Written words	25/30*	29/30
Written sentences	23/32[a]	28/32
Expressive language		
Repetition		
Words	30/32	30/32
Complex words	4/6*	5/6[a]
Nonwords	6/10	8/10
Digit string span	6	6
Sentences	12/12	12/12
Naming		
Objects	37/48*	28/48*
Actions	10/10	4/10*
Reading		
Words	46/48	44/48*
Complex words	4/6[a]	6/6
Function words	6/6	6/6
Nonwords	10/10	6/10[a]
Writing		
Copying	10/27*	27/27
Picture names	20/21	14/21*
Dictation	27/28	27/28

Note. CAT = Comprehensive Aphasia Test (Swinburn et al., 2004).
[a]Borderline between intact and impaired functioning. Norms were obtained from the CAT manual (Swinburn et al., 2004).
*Below the cutoff for intact functioning.

may have been additional impairments in the phonological input lexicon (see Tables 1 and 2 for more information). Similarly, frequency effects in spoken naming and better performance on the PALPA auditory synonym judgment task compared with the BNT suggested that there may have been further impairments in the representation of lexical items within the phonological output lexicon or in the access to the lexical items from the semantic system (Nickels, 2001; Whitworth et al., 2005).

P2 was a 68-year-old, female, retired high school drama teacher with 15 years of education. P2 presented at hospital in June 2004 with a left embolic stroke involving the middle cerebral artery. At the time of the present study, P2's language production was fluent. P2's errors on the BNT at this time consisted primarily of no responses. Phonemic cues were of some benefit, with 19/34 phonemic cues being effective (see Table 1). Language assessments indicated that P2 experienced greater difficulty naming verbs compared with nouns, although both were impaired. P2's performance on an auditory lexical decision task suggested that her phonological input lexicon was intact (Kay et al., 1992). The presence of imageability effects on the auditory synonym judgment task, but good performance on the semantic memory and word comprehension tasks suggested a mild impairment at the lexical–semantic level (Cole-Virtue & Nickels, 2004; Howard & Gatehouse, 2006). Additionally, the representation of items within P2's phonological output lexicon or the link between the semantic system and the phonological output lexicon may have been impaired as (a) phonemic cues facilitated naming, (b) P2's naming was sensitive to word frequency, (c) P2's spoken naming was poorer than her written naming, (d) P2's performance on the BNT was poorer than expected based on her performance on the auditory synonym judgment task, and (e) circumlocutions were present in P2's naming errors (Howard & Gatehouse, 2006; Nickels, 2001; Whitworth et al., 2005; see Tables 1 and 2 for more information).

Before inclusion in the study, P1 and P2 completed a medical examination (including a blood test and an electrocardiogram) with a general practitioner. In addition, they were given a trial dose of dexamphetamine and monitored for side effects, none of which occurred. Both participants had previously received treatment for anomia; however, they did not receive any anomia treatment from outside sources while participating in study. Both P1 and P2 provided written consent for participation in study.

Experimental Stimuli

The experimental stimuli consisted of black-and-white line drawings of real objects from Snodgrass and Vanderwart (1980), the International Picture-Naming Project (Szekely et al., 2004), and An Object and Action Naming Battery (Druks & Masterson, 2000). The names ranged from one to four syllables, and represented a combination of low, medium, and high frequency words.

Experimental Procedure

The study was conducted in accordance with the Declaration of Helsinki. Ethical clearance was obtained from the University of Queensland Medical Research Ethics Committee, the Queensland Health Human Research Ethics Committee, and the Human Research Ethics Committees of individual hospitals.

Pretreatment procedures

Each participant attended three pretreatment sessions. During the pretreatment sessions, participants completed a battery of language and neuropsychological assessments (see Tables 1 and 2) and attempted to name the experimental stimuli. Each participant attempted to name the stimuli (403 items for P1 and 300 items for P2) on two separate occa-

sions (P1 was required to name extra items so that sufficient items were available for use as treatment items). The stimuli were presented one-by-one on a laptop computer. A response was scored as correct if the name of the object was produced within 5 seconds. As per previous studies (e.g., Drew & Thompson, 1999; Howard et al., 1985a), responses where a single phoneme was added, substituted, distorted, or omitted were scored as correct. All other responses were scored as incorrect.

Based upon individual pretreatment performance, experimental items were selected to use as treatment stimuli for each participant (140 for P1 and 124 for P2). The items were divided into the following conditions for P1: Set A [30 incorrectly named pictures, 30 incorrectly named control pictures, and 10 correctly named pictures (total n = 70)] and Set B [30 incorrectly named pictures, 30 incorrectly named control pictures, and 10 correctly named pictures (total n = 70)]. For P2, the items were divided into the following conditions: Set A [31 incorrectly named pictures and 31 incorrectly named control pictures (total n = 62)] and Set B [31 incorrectly named pictures and 31 incorrectly named control pictures (total n = 62)]. Within and across each set, the treated and untreated (control) pictures were matched for frequency (Francis & Kucera, 1982) (where available), word length, and number of syllables (all $p >$ .10). During the pretreatment sessions, participants also completed a control task (nonword reading) on two separate occasions.

Treatment Procedures

Participants attended two 4-week blocks of morning therapy sessions (two to three sessions per week) for a total of 10 sessions per block. While we acknowledge that Bhogal and colleagues (2003) recommended that individuals with aphasia should receive an intense block of therapy (approximately 8.8 hours of therapy per week for 11.2 weeks), we designed our study to reflect current therapy practice for individuals who are in the chronic recovery stage post-stroke. The therapy blocks were separated by a 4-week washout period during which no anomia therapy or dexamphetamine was received. Each participant received two 5-mg dexamphetamine tablets during one therapy block and two matched placebo tablets during the other therapy block. Participants were given the tablets by a nurse approximately 1.75 hours before commencing the therapy tasks each session. This time period was selected so that optimal dexamphetamine plasma levels were reached during the therapy tasks (Angrist et al., 1987; Asghar et al., 2003). The participants and the speech pathologist running the sessions were blinded as to whether the participants received the dexamphetamine or placebo each session.

The therapy component of each session lasted approximately 45 minutes. As per previous research (e.g., Drew & Thompson, 1999; Nettleton & Lesser, 1991; Nickels, 2002), we decided to use a multimodal approach to treatment to address the different levels of breakdown. Participants completed a pseudorandomized selection of computer-based therapy tasks each session from a battery of tasks, including (a) word-picture matching (participants pointed to the picture that matched a spoken word from a choice of four pictures and then repeated the word), (b) yes/no semantic judgments (participants responded yes/no to questions about the semantic features of items, e.g., is a fork used for eating?), (c) naming with a phonemic cue (participants named pictures of objects when verbally given the first sound in the word), (d) word repetition (participants repeated the name of an item when presented with a picture of the item and a verbal model), (e) counting syllables and phonemes (participants counted the number of sounds or syllables in words when given a picture of the item and the spoken name), and (f) re-arranging anagrams (participants rearranged letters to spell the item names when given a picture of each item and scrambled letters in the item's name). Participants were corrected for errors during the tasks. Each participant completed each therapy task the same number of times in blocks one and two. Participants completed three tasks each session with all of the items within one set of stimulus items (A or B). For each participant, the stimulus items in Set A were treated during one therapy block and the stimulus items in Set B were treated during the other block. The order of the therapy tasks and the order of the stimuli for each task were randomized each session. All therapy tasks were presented using E-prime experimental software (Psychology Software Tools, Pittsburgh, PA).

At the start of every third therapy session, participants were tested on all the pictures within the set being targeted during that therapy block (treated and untreated). For a response to be correct, the object had to be named within 5 seconds. Where participants offered multiple answers, only the first answer was scored. Participants were re-assessed with both Sets A and B in their entirety at the end of the washout period and at the end of the second therapy block. The control task was completed at the same time as the naming probes. Different matched sets of nonwords were used in blocks one and two.

Posttreatment Procedures

Participants were re-assessed with each set 1 day and 1 month after completing each therapy block. The control nonnaming task (nonword reading) was also completed during these sessions.

Data Analysis

For both participants, the proportion of correct responses on the naming and nonword reading tasks was analyzed using *Z* tests, as per Zou et al. (2003) and Bordens and Abbott (1991). As per previous research, for data pertaining to naming accuracy, only items that were named incorrectly during the baseline sessions were included in the analyses (e.g., Best et al., 2002; Howard et al., 1985b; Miceli et al., 1996). An α level of .05 was used for all analyses.

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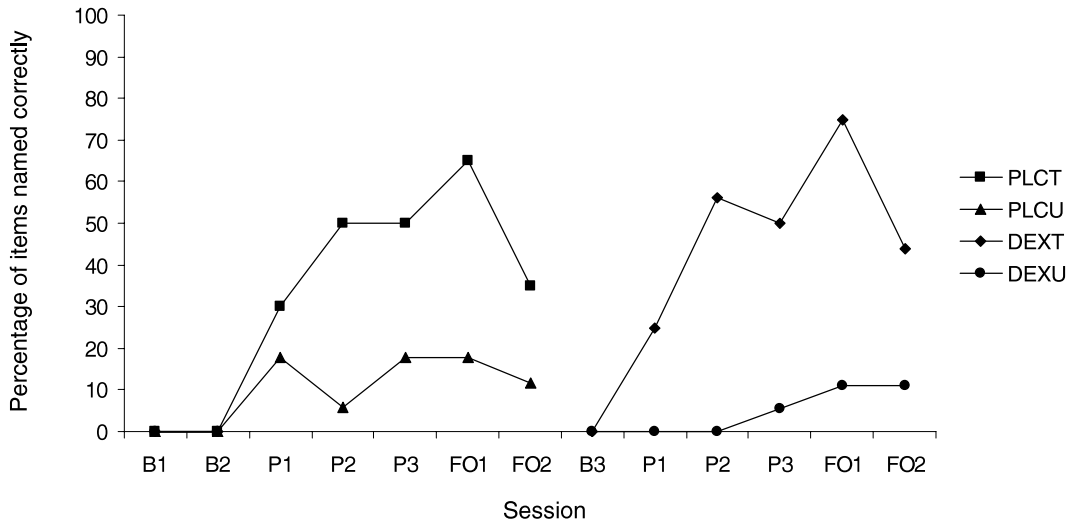

Fig. 1. Percentage of items named correctly by P1 under dexamphetamine and placebo. DEX, Dexamphetamine; PLC, placebo; T, treated; U, untreated; B, baseline; P, probe; FO, follow-up.

The physiological measures *blood pressure* and *heart rate* were analyzed descriptively by calculating means and standard deviations.

RESULTS

P1

Naming

By the end of each therapy block, P1 correctly named treated items under dexamphetamine more accurately than items treated under placebo, however, the difference was not statistically significant ($p > .05$; see Figure 1). The difference was still present 1 month later, but remained statistically nonsignificant (see Figure 1). Treated items were named more accurately than untreated items by the end of both therapy blocks (Dexamphetamine: $Z = 4.886$, $p < .001$; Placebo: $Z = 3.319$, $p < .001$), with the difference still present 1 month later (see Figure 1). There was no difference between dexamphetamine or placebo untreated items at the end of the therapy blocks ($p > .05$).

Control task

For P1, there was no significant difference in the number of nonwords read correctly under dexamphetamine compared with placebo at baseline, during the probe sessions, or at follow-up ($p > .05$). Within each therapy block, the number of nonwords read correctly by P1 did not change significantly between the baseline, probe, and follow-up sessions (all $p > .05$).

Physiological measures

Overall, P1's blood pressure (systolic and diastolic) increased marginally between baseline and the start of the therapy tasks under dexamphetamine, but decreased marginally under placebo (see Table 3). P1's heart rate increased slightly under dexamphetamine and placebo, with a slightly greater increase occurring under dexamphetamine (see Table 3).

Table 3. Average blood pressure and heart rate measurements during each therapy session

		Pre-tablet			Pre-therapy (1.75 hours later)		
Participant		BPs	BPd	HR	BPs	BPd	HR
P1	DEX	132.00 (5.87)	62.00 (3.50)	66.00 (5.73)	134.50 (7.62)	63.50 (7.47)	69.40 (5.17)
	PLC	124.00 (10.75)	64.50 (8.96)	66.80 (6.88)	121.20 (6.14)	62.00 (5.87)	67.20 (10.51)
P2	DEX	110.00 (8.50)	68.50 (7.47)	59.60 (8.93)	104.00 (9.94)	67.00 (6.32)	67.40 (6.40)
	PLC	98.50 (6.69)	59.50 (4.97)	62.00 (6.99)	97.00 (3.50)	60.50 (1.58)	62.60 (8.59)

Note. DEX = dexamphetamine; PLC = placebo; BPs = systolic blood pressure; BPd = diastolic blood pressure; HR = heart rate. Standard deviations are provided in brackets.

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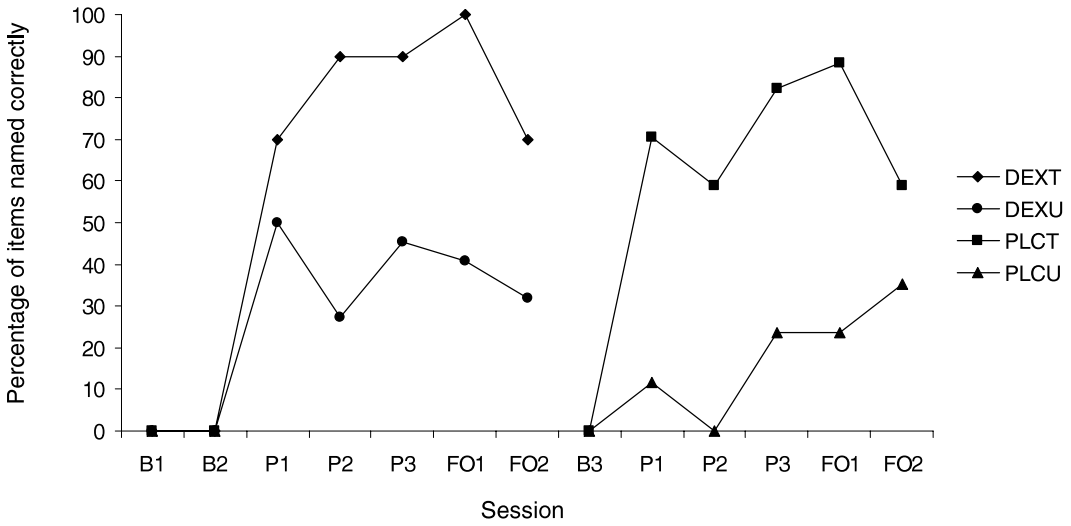

Fig. 2. Percentage of items named correctly by P2 under dexamphetamine and placebo. DEX, Dexamphetamine; PLC, placebo; T, treated; U, untreated; B, baseline; P, probe; FO, follow-up.

P2

Naming

By the end of each therapy block, P2 correctly named treated items under dexamphetamine more accurately than items treated under placebo ($Z = 1.523$; $p = .032$), with the difference still present 1 month later (see Figure 2). Treated items were named more accurately than untreated items by the end of both therapy blocks (Dexamphetamine: $Z = 5.627$, $p < .001$; Placebo: $Z = 4.917$; $p < .001$), with the difference still present 1 month later (see Figure 2). There was no difference between dexamphetamine or placebo untreated items at the end of the therapy blocks ($p > .05$).

Control task

There was no significant difference in the number of nonwords read correctly by P2 under dexamphetamine compared with placebo at baseline, during the probe sessions, or at follow-up ($p > .05$). Within each therapy block, the number of nonwords read correctly by P2 did not change significantly between the baseline, probe, and follow-up sessions (all $p > .05$).

Physiological measures

Under dexamphetamine, P2's blood pressure (systolic and diastolic) decreased slightly between baseline and the start of the therapy tasks. Under placebo, P2's systolic blood pressure also decreased during this time; however, her diastolic blood pressure increased marginally (see Table 3). P2's heart rate increased under dexamphetamine but not under placebo (see Table 3).

DISCUSSION

The present study suggests that dexamphetamine might improve language treatment effects in some individuals with chronic aphasia. This finding contrasts with research which has suggested that dexamphetamine can enhance language recovery in the acute stage poststroke (Walker-Batson et al., 1992, 2001), but not in the chronic recovery stage (McNeil et al., 1997; Walker-Batson et al., 2004), a phenomenon that has been attributed to the drug's neuromodulatory effects on brain plasticity during the early recovery stage (de Boissezon et al., 2007; Walker-Batson et al., 2004). Thus, the present study suggests that combined dexamphetamine and behavioral therapy may be of benefit for some individuals who have reached a plateau in traditional behavioral therapy, but still experience stroke-related naming difficulties.

As discussed previously, Nadeau and Wu (2006) suggested that dexamphetamine may act as an adjuvant to enhance treatment effects when rehabilitation involves normal learning processes; however, the exact mechanisms through which this occurs are unknown. That P1 and P2 did not improve significantly on the control task (nonword reading) suggests that the effects of dexamphetamine were not due to a generalized improvement in language functioning and were specific to learning. That dexamphetamine appeared to improve treated but not untreated items provided further suggestion for a role for dexamphetamine in the re-learning of specific lexical items. Indeed, research with healthy adults has found that dexamphetamine can improve new word learning and later retrieval (Breitenstein et al., 2004; Whiting et al., 2007a,b). It is possible that dexamphetamine may have acted by improving attentional mechanisms or consolidation of the items within long-term memory (Soetens et al., 1993, 1995; Stefanatos et al., 2006); however, further research is required. Similarly, it is not possible to dissociate the precise neurophysiological basis for the observed effects (See Breitenstein et al., 2004; Knecht et al., 2004 for a more detailed discussion of this issue). Unfortunately we were not able to measure the generalization of treatment effects to everyday living; however, this should be a direction for future research.

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The statistical test of proportions used in our study (Zou et al., 2003) is normally used to test proportions involving populations of individuals, in which one can safely assume lack of statistical interdependence among the treated items (individual subjects) with respect to drug effect. In the present study, the individual items were words and lack of statistical interdependence with respect to drug effect cannot be assured.

As a final note, neither P1 nor P2 experienced adverse effects from dexamphetamine. It is important to note that P2 reached ceiling levels (i.e., 100% items named correctly) at the completion of the therapy under dexamphetamine. Thus, if more items were included in the naming battery, it is possible that P2 may have displayed an even greater improvement on items treated under dexamphetamine compared with placebo. As the present study consisted of two case studies and only modest treatment effects were observed, further research involving a greater number of participants is warranted. Further research is also required to systematically compare whether dexamphetamine is more effective as an adjunct to behavioral naming therapy in the acute or chronic recovery stages poststroke and to investigate which symptoms and treatments are most responsive to pharmacotherapy.

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