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A double-blind, placebo-controlled study of pharmacological and behavioural treatment of lexical–semantic deficits in aphasia

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Abstract

This investigation replicated and extended an earlier study of naming disorders (McNeil *et al.* 1995) by administering a placebo and pharmacological agents (*d*-amphetamine and selegiline) in the presence and absence of a behavioural intervention termed lexical–semantic activation inhibition therapy (L-SAIT) to examine their effects on naming performance in two adults with stroke-induced aphasia. Results revealed acquisition and maintenance effects of L-SAIT on targeted lexical items, no effects of placebo or active pharmacological agents in the absence of L-SAIT, and no differential effects between placebo + L-SAIT and pharmacological agents + L-SAIT. Thus, positive treatment effects were attributed to L-SAIT. Generalization to untrained items within and across form class was not observed, nor was generalization to measures of informativeness of connected speech. Subject 1 evidenced improvement on the Rapid Automatized Naming Test (Denckla and Rudel 1976).

Introduction

Disorders of the lexical/semantic level of language (dysnomia or naming disorders) are present in all types of aphasia, regardless of classification system used. Naming disorders are often the presenting sign or symptom of aphasia, dementia, confusion, and a host of other cognitive disorders. Naming disorders are also frequently found in developmental language and learning disorders. Their importance to inter- and intra-personal communication is eminent. As such, the treatment of naming disorders has received perhaps more attention than any other area of language or communication disorder.

The theoretical motivations for, and methods of treating, dysnomia are relatively finite. From the theoretical end, Lesser (1989), among others, has drawn the critical distinction between cognitive–linguistic processing involved in visual or object/picture naming and those processes involved in naming during selective retrieval or conversational activities. Further, current notions of dysnomia are well unified in their specification that two linguistic sources of selective retrieval or conversational

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dysnomia include those generated by a failure of lexical–semantic processes or those generated by a failure of phonological processes (Hadar *et al.* 1987, Howard *et al.* 1985, Lesser 1989).

The selection of treatment tasks for dysnomia has frequently comprised those involved in picture naming (e.g. Hillis 1989, Seron *et al.* 1979) or word reading (e.g. Seron *et al.* 1979, Thompson and Kearns 1981). Although internally generated word tasks are commonly used for testing dysnomia (e.g. word fluency tasks), rarely have such tasks been used as part of the treatment. The targets for dysnomia treatment have varied considerably among researchers. Most investigators have selected targets based on form class (Hillis 1989, Seron *et al.* 1979, Thompson and Kearns 1981). Some investigators have selected exemplars based on semantic features (Thompson and Kearns 1981) or phonological relatedness (Hillis 1989). Most investigators also control for word length, frequency, abstractness, operativity, imageability, and a host of other psycholinguistic factors known to influence lexical performance. After the tasks and targets are selected for treatment, investigators select the techniques to be utilized for facilitating the acquisition, generalization and maintenance of targets. These facilitating techniques generally take the form of either multiple stimulus repetitions (Brookshire 1975), or subjects' erred responses are cued until they are produced correctly (Rochford and Williams 1962, Linebaugh and Lehner 1977).

The theoretical motivation for pharmacological treatment as an adjunct to behavioural therapies is derived primarily from the animal literature. Animal models of experimental stroke suggest a role for endogenous and exogenous catecholamines in motor recovery. Although evidence implicates both norepinephrine (NE) and dopamine (DA) in this process, the strongest data support a role for NE. Pharmacologically, the drug dextro-amphetamine increases the concentration of both of these catecholamines at the postsynaptic junction (Cooper *et al.* 1991). The drugs bromocriptine and selegiline affect DA but not NE. Whereas bromocriptine acts as an agonist of DA, seligiline acts to decrease metabolism of endogenous DA by blocking its degradation by monoamine oxidase type B. Both dextro-amphetamine (Walker-Batson *et al.* 1991) and bromocriptine (Albert *et al.* 1988, Bachman and Morgan 1988, Gupta and Mlcoch 1991, MacLennan *et al.* 1991) have been used in human studies of aphasia therapy with uninterpretable results.

There are several factors that may account for the equivocal results of the pharmacological intervention in aphasia to date. As noted by MacLennan *et al.* (1991), the Albert *et al.* (1988) and Bachman and Morgan (1988) studies failed to include baseline or reliability measures for their dependent variables, did not blind investigators regarding administration of the pharmacological agent, and did not incorporate a placebo phase in their experimental designs (i.e. they did not blind the subject to the drug). Subsequent studies reporting positive effects of bromocriptine (Gupta and Mlcoch 1991) also reported open-label designs. The Walker-Batson *et al.* (1991) study examining the effects of *d*-amphetamine on verbal performance had similar limitations, as well as several other obvious confounds such as concurrent language therapy and an absence of experimental control for physiological recovery.

McNeil *et al.* (1995) reported the results of a lexical–semantic treatment for a patient with primary progressive aphasia that combined *d*-amphetamine therapy and a behavioural treatment termed lexical–semantic activation inhibition treatment (L-SAIT). Dextro-amphetamine was administered in divided doses that were

scheduled to peak during periods of treatment and probe data collection. The behavioural treatment consisted of the oral presentation of predicative adjectives and eliciting either an antonym or synonym for the word or phrase. Failed responses were cued with the Linebaugh (1990) cueing hierarchy. Results of this treatment regimen were effective for acquisition of both antonyms and synonyms of trained predicate adjectives, although extended practice was required to achieve criterion. Generalization to non-treated adjectives, verbs, and prepositions was observed, and maintenance was observed but was difficult to disambiguate from the progressive nature of the patient's disease. Differential effects between L-SAIT alone and L-SAIT + *d*-amphetamine treatment were not observed. It should be noted that the design of this study also failed to incorporate procedures to blind the patient and the clinician to the pharmacological agent. However, this design did allow for an examination of the differential effects of the pharmacological agent plus behavioural treatment and the behavioural treatment alone.

This investigation sought to partially replicate and extend the findings from the McNeil *et al.* (1995) investigation by including a double-blind placebo component to the experimental design, by administering the treatment to subjects with stable stroke-induced aphasia, and by administering selegiline as an alternative to the *d*-amphetamine in one of the two subjects. Research questions were: Is there a differential rate of acquisition for treated items across experimental phases? Is there maintenance of positive treatment effects with the withdrawal of all treatment? Does generalization extend to untreated members of the same form class, across form classes, to a structured naming task and to a discourse-level production task?

Method

Subjects

Two adult males with aphasia and co-occurring apraxia of speech participated in the investigation. The diagnoses of aphasia and apraxia of speech were based upon clinical criteria specified by Darley (1982), and Wertz *et al.* (1984) respectively. Both diagnoses were determined by clinical examination and formal testing conducted by the investigators.

Subject 1 was a 55-year-old, left-handed, retired business manager with 13 years of formal education. At the time of his enrolment in the study he was living independently and was 3 years post-onset of a single, thromboembolic L-MCA stroke with residual aphasia, apraxia of speech, and right hemiparesis. His performance on the Western Aphasia Battery (WAB) (Kertesz 1982) met classification criteria for anomic aphasia and resulted in an aphasia quotient of 79. Overall performance on the Porch Index of Communicative Abilities (PICA) (Porch 1981) placed him in the 89th percentile of left hemisphere-damaged adults, with sentence formulation (VRB-I, GPH-A), sentence completion (VRB-IX), and writing words to dictation (GPH-B) subtests accounting for the greatest performance deficits. Performance on the Test of Adolescent/Adult Word Finding (TAWF) (German 1990) placed him below the 1st percentile for age-matched normal adults, and was characterized primarily by response rejections (i.e. 'I don't know'), and occasional semantic paraphasias (i.e. crutch/cane, telescope/microscope). Only one error response appeared to have been attributable to apraxic and/or phonological impairment (i.e. funnel/flannel). Performance on the Apraxia Battery for Adults (ABA) (Dabul 1986) revealed the presence of apraxic speech

Table 1. Biographical and standardized test information

Subject 1	Subject 2
55 years old	63 years old
Left-handed	Right-handed
Retired business manager	Retired business owner
13 years education	14 years education
3 years post-onset left MCA CVA	19 years post-onset of left MCA CVA
PICA: 13·76 (89th percentile)	PICA: 13·33 (86th percentile)
RTT: 13·72 (86th percentile)	RTT: 11·74 (43rd percentile)
RCBA: 89/100	RCBA: 88/100
RAVEN'S: 27/36	RAVEN'S: 28/36
WAB-AQ: 78·96	WAB-AQ: 87·5
TAWF: 60 (0·1 percentile)	TAWF: 91 (46th percentile)
DCT: 68/80	DCT: 67/80
BDI: 3 (not depressed)	BDI: 3 (not depressed)

Note. PICA = Porch Index of Communicative Ability; RTT = Revised Token Test, RCBA = Reading Comprehension Battery for Aphasia; Raven's = Raven's Progressive Colored Matrices; WAB-AQ = Western Aphasia Battery, Aphasia Quotient; TAWF = Test of Adult Word Finding; DCT = Discourse Comprehension Test; BDI = Beck Depression Inventory.

behaviours demonstrated on increasing word length, and connected speech/reading subtests only. Performance on these subtests met the 'mild to moderate' severity criteria of the instrument.

Subject 2 was a 63-year-old, right-handed, retired business owner and professional musician with 14 years of formal education. At the time of his enrolment in the study he was living with his spouse of 3 years, and was 19 years post-onset of a single, thromboembolic L-MCA stroke with residual aphasia, apraxia of speech, and right hemiparesis with greater involvement of the lower extremity. His performance on the WAB (Kertesz 1982) met classification criteria for anomic aphasia and resulted in an aphasia quotient of 87·5. Overall performance on the PICA (Porch 1981) placed him in the 86th percentile of aphasic adults with sentence formulation (VRB-I, GPH-A), writing words to dictation (GPH-B), and writing words spelled by the examiner (GPH-C) accounting for the greatest performance deficits. Performance on the TAWF (German 1990) placed him within the 46th percentile for age-matched normal adults and was characterized primarily by semantic paraphasias (i.e. calculator/computer, jockey/thoroughbred, thermos/bottle, measuring/marking). Performance on the ABA (Dabul 1986) revealed the presence of apraxic speech behaviours demonstrated on increasing word length and connected speech/reading subtests only. Performance on these subtests met the 'mild to moderate' severity criteria of the instrument. Table 1 lists subjects performance on additional speech and language measures administered at the initiation of the treatment trial.

Design

A single-subject, double-blind placebo-controlled multiple-baseline design incorporating placebo/drug comparisons in the presence and absence of L-SAIT was employed to examine the effects of these variables on subjects' word-retrieval

performance. Repeated measurement of subjects' verbal production of trained and untrained synonyms and antonyms for independent lists of adjectives, verbs, nouns, and prepositions served as the primary dependent variables. In addition, the Rapid Automatized Naming Test (Denckla and Rudel 1976) and measures of the informativeness of connected discourse (Nicholas and Brookshire 1993) were measured repeatedly throughout the study. Following the establishment of base rates for all word lists, subjects received consecutive 3-week trials of (a) placebo, (b) pharmacotherapy, (c) placebo + L-SAIT, and (d) pharmacotherapy + L-SAIT. Probes were conducted at the beginning of treatment sessions, twice a week across each phase of treatment. The collection of baseline and probe data consisted of orally presenting the subjects with lexical items from all lists and asking them to produce either antonyms or synonyms for the word. Feedback about performance and cues for erred responses were not given during the collection of baseline or probe data.

Figures 1, 2, 5, and 6 illustrate the basic structure of the design. Inspection of these figures reveals that word lists categorized by form class occupy the ordinate with the percentage of correct productions specified for treated and untreated lists. The top abscissa specifies the six experimental phases and the bottom abscissa specifies the dates on which the probe data were collected. The filled arrow represents the initiation of L-SAIT to a specific form class list of 10 lexical items. The unfilled arrow represents the achievement of criterion.

Placebo/pharmacotherapy

All medication capsules had the same physical appearance and were administered according to the identical schedule whether active drug or placebo was used, and whether or not L-SAIT was being administered concurrently. Adverse effects were monitored by a physician (S. L. S.) who was not blinded to the specific drug. Subjects and the speech–language pathologist (K. A. S.) who administered L-SAIT and dependent measures were blinded as to whether the active drug or the placebo was being administered at any given time. Dextro-amphetamine was administered to Subject 1 at 2·5 mg twice a day, escalating the dosage to 10 mg twice a day. This dosage represents the dose used in a well-designed and effective outcome study of motor rehabilitation in elderly patients (Crisostomo *et al.* 1988). Selegiline was administered to Subject 2 at a dose of 5 mg once a day and increased to 5 mg twice a day, which is the accepted dose for treatment of early-stage Parkinson's disease. Both subjects received placebo for 21 consecutive days during the second and fourth phases of the study and their respective active drug for 21 consecutive days during the third and fifth phases of the study. Again, doses were scheduled to peak during probe/treatment sessions.

L-SAIT

Both subjects received L-SAIT as described in McNeil *et al.* (1995) during the fourth and fifth phases of the study. L-SAIT was administered three or four times per week over a 6-week period. Subjects 1 and 2 completed 19 and 20 treatment sessions respectively. Each treatment session consisted of three blocks of 10 trials on two separate lists for a total of 60 treatment trials per session. Each trial consisted of orally presenting subjects with a lexical item within a particular form

class and asking them to produce the antonym or synonym for that word. When failure to produce the correct antonym or synonym occurred, a cueing hierarchy based on the work of Linebaugh (1990) was used in an attempt to evoke the correct answer. Each response was scored as accurate or inaccurate within a 5-second delay. Criteria for termination of treatment on a particular list were 80% accuracy for three consecutive sessions, or 80% accuracy at scheduled phase changes.

Results

Subject 1

Antonyms

Subject 1's performance on the antonym generation task is displayed in Figure 1. Inspection of these data reveals variable performance during each of the first three experimental phases for most word lists. During the placebo + L-SAIT phase, adjective list 1 was trained. Inspection of the data during this phase reveals improved performance relative to previous experimental phases with criterion achieved during the fifth probe session. Adjective list 2 was trained during the *d*-amphetamine + L-SAIT phase. Inspection of these data reveals immediate and differentiable gains above previous experimental phases. However, criterion was *not* met prior to the termination of this phase. Generalization of treatment gains to lists within and across form classes was *not* evident. Maintenance of treatment gains for the two adjective lists *was* evident, although there *was* the suggestion of a diminution of gains at the final probe. Performance did not change relative to baseline with the administration of either placebo or *d*-amphetamine in the absence of L-SAIT.

Synonyms

Figure 2 displays baseline and probe data for the synonym generation task. This task was more difficult than the antonym task for this subject (and all subjects), as evidenced by lower and relatively stable base rates across form class lists. In addition, no changes in performance relative to baseline were observed on any lists with the administration of either placebo or *d*-amphetamine in the absence of L-SAIT. However, when adjective list 1 was targeted during the placebo + L-SAIT condition, performance on that list improved and criterion was met during the fifth probe session. Similarly, there was an immediate and substantive improvement in performance on adjective list 2 with the initiation of L-SAIT during the L-SAIT + *d*-amphetamine phase. Nevertheless, criterion was *not* met prior to the scheduled temporal termination of this phase. As with the antonym task, generalization of treatment gains to lists within and across form classes did *not* occur. Maintenance of treatment gains for the two adjective lists *was* evident.

Rapid Automatized Naming Test

Figure 3 illustrates Subject 1's performance on the combined subtest of the Rapid Automatized Naming (RAN) Test (Denckla and Rudel 1976) across all phases of the study. A generalization effect was evident in the form of decreased errors with the initiation of L-SAIT during the placebo + L-SAIT phase and continued through the *d*-amphetamine + L-SAIT phase. The decrease in lexical selection errors does not represent a time/accuracy trade-off, as the time measured in seconds did not

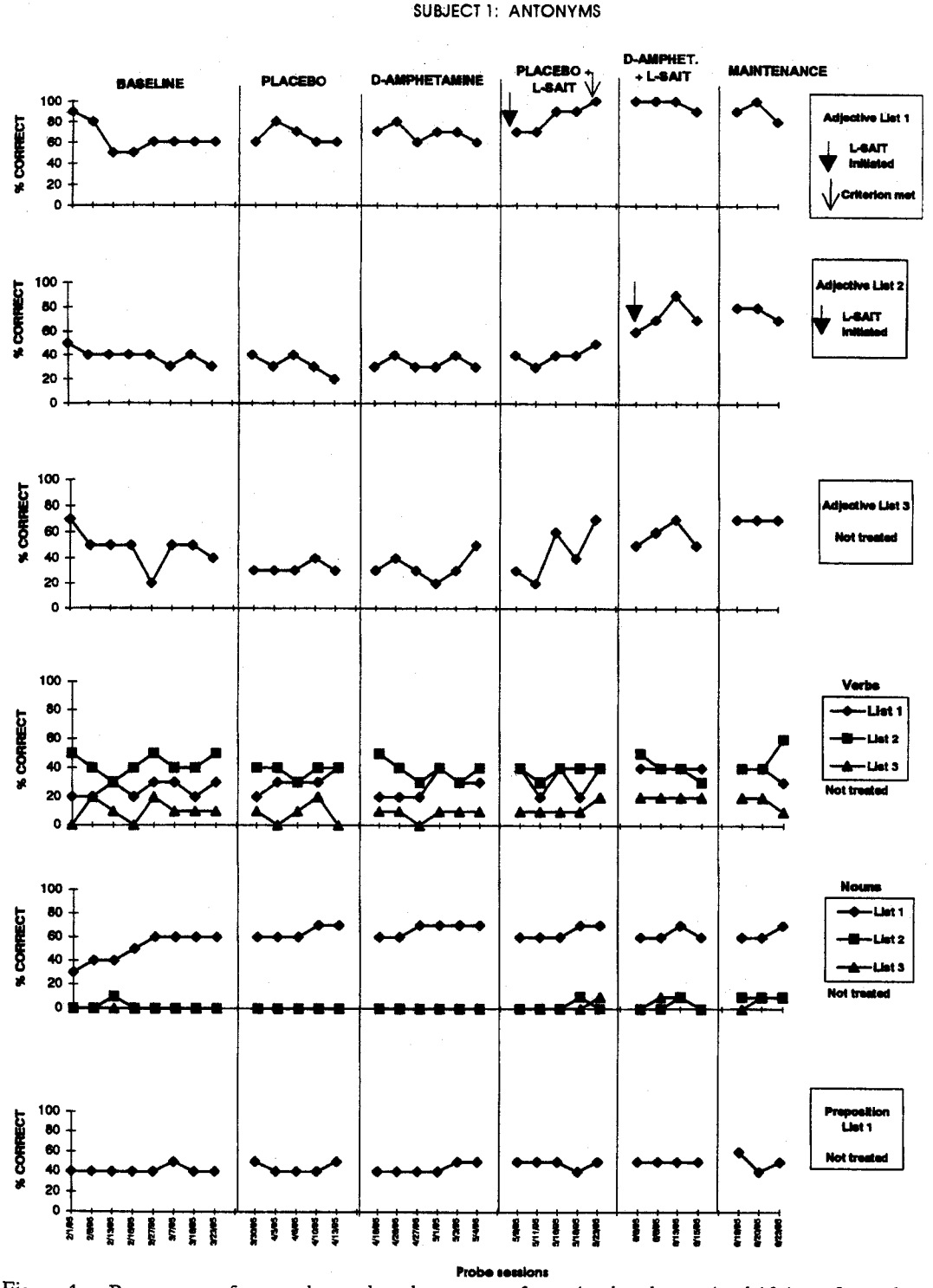

Figure 1. Percentage of correctly produced antonyms for trained and untrained 10-item form class lists across all experimental phases. *Note.* L-SAIT = lexical–semantic activation inhibition therapy.

differ across phases relative to baseline levels. This effect was maintained at a single probe 1 week following the final phase of treatment. In addition, performance did not change relative to baseline levels with the administration of either placebo or *d*-amphetamine in the absence of L-SAIT.

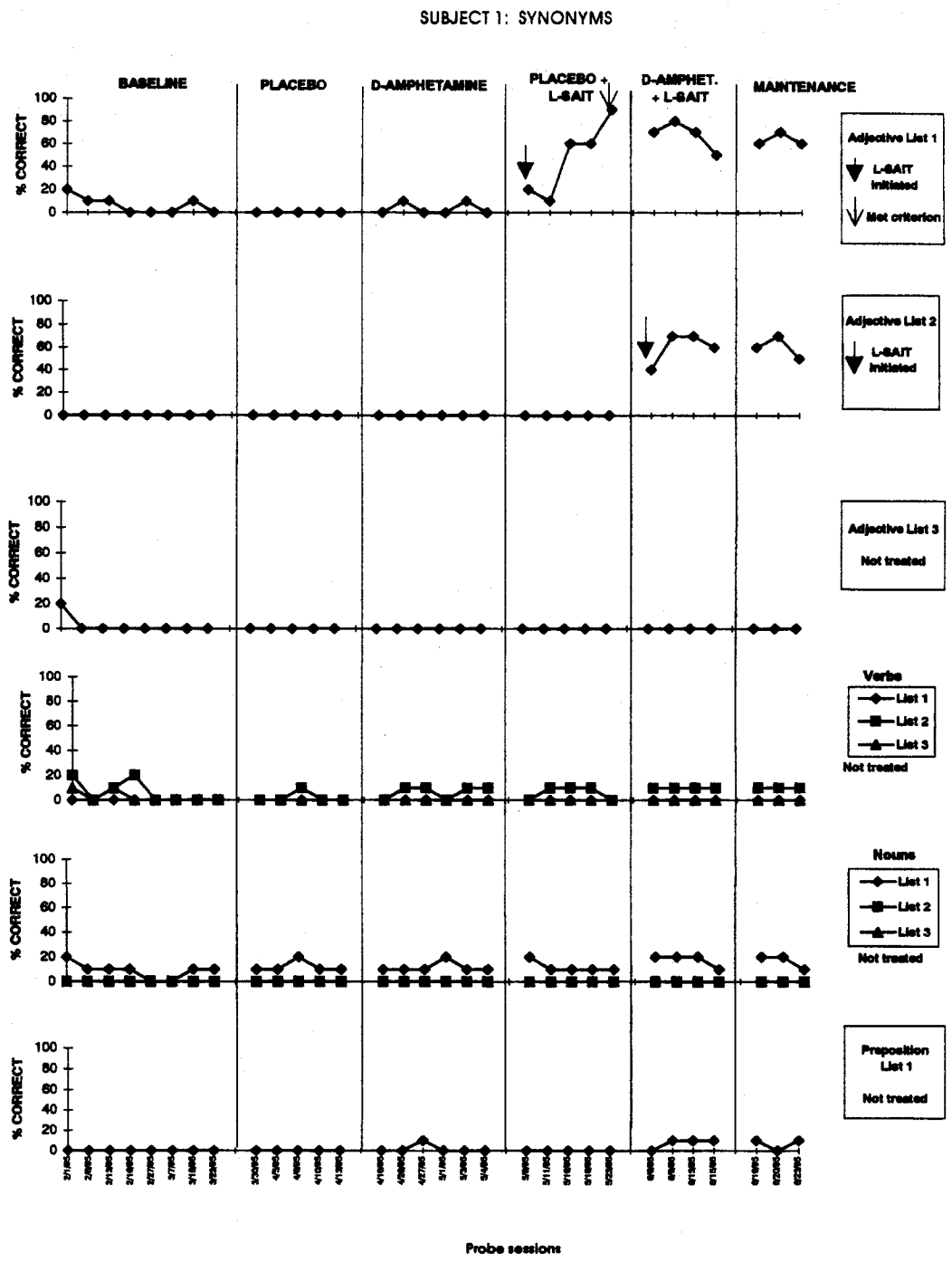

Figure 2. Percentage of correctly produced synonyms for trained and untrained 10-item form class lists across all experimental phases. *Note.* L-SAIT = lexical–semantic activation inhibition therapy.

Information content

Figure 4 displays Subject 1's performance on measures of verbal productivity and informativeness (Nicholas and Brookshire 1993) derived from connected speech samples collected across all experimental phases. No substantive change in performance was evident for either metric during the course of the investigation.

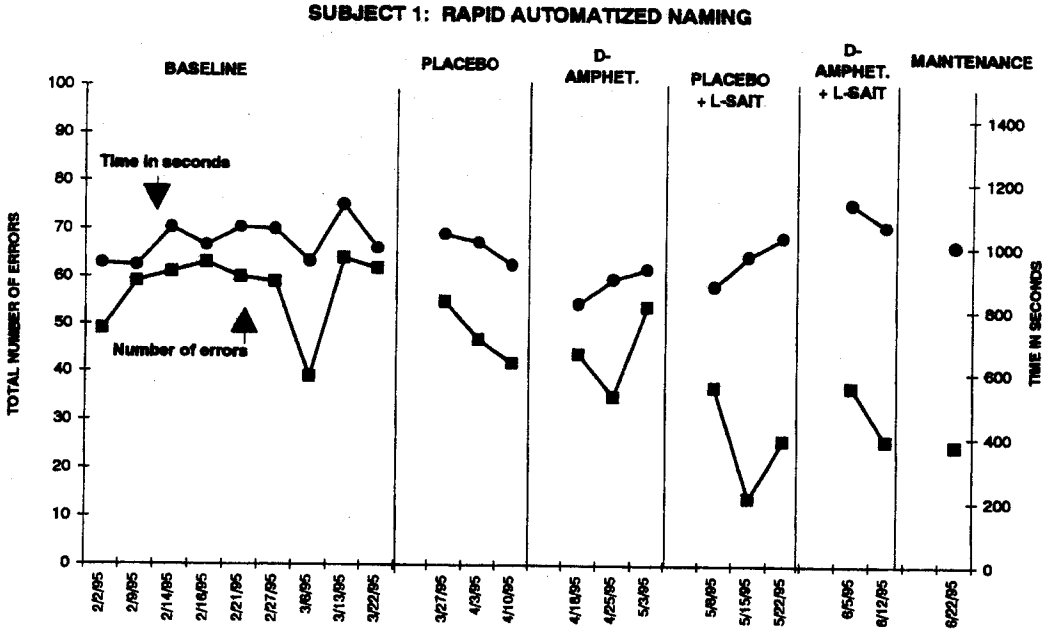

Figure 3. Number of naming errors and the time in seconds to complete the combined subtest of the Rapid Automatized Naming Test (Denckla and Rudel 1976). *Note.* L-SAIT = lexical–semantic activation inhibition therapy.

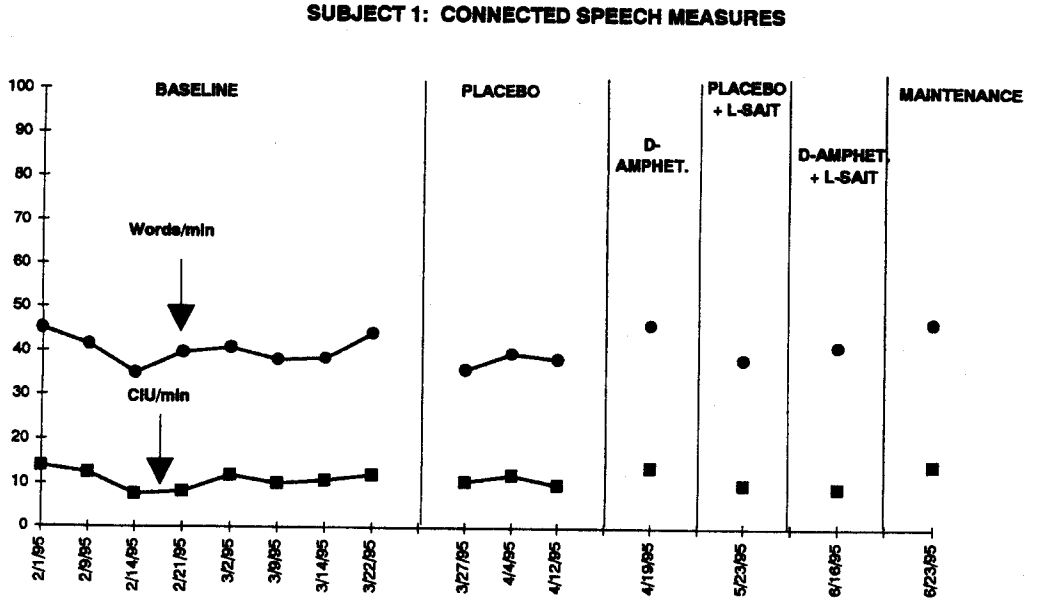

Figure 4. Words per minute and correct information units per minute (CIU/min) derived from samples of connected speech (Nicholas and Brookshire 1993). *Note.* L-SAIT = lexical–semantic activation inhibition therapy.

Subject 2

Antonyms

Subject 2's performance on the antonym generation task is displayed in Figure 5. These data reveal variability in the level and stability of subject's performance across lists, and across the first three experimental phases. Inspection of the data for adjective lists 1 and 2 reveals performance levels close to ceiling throughout

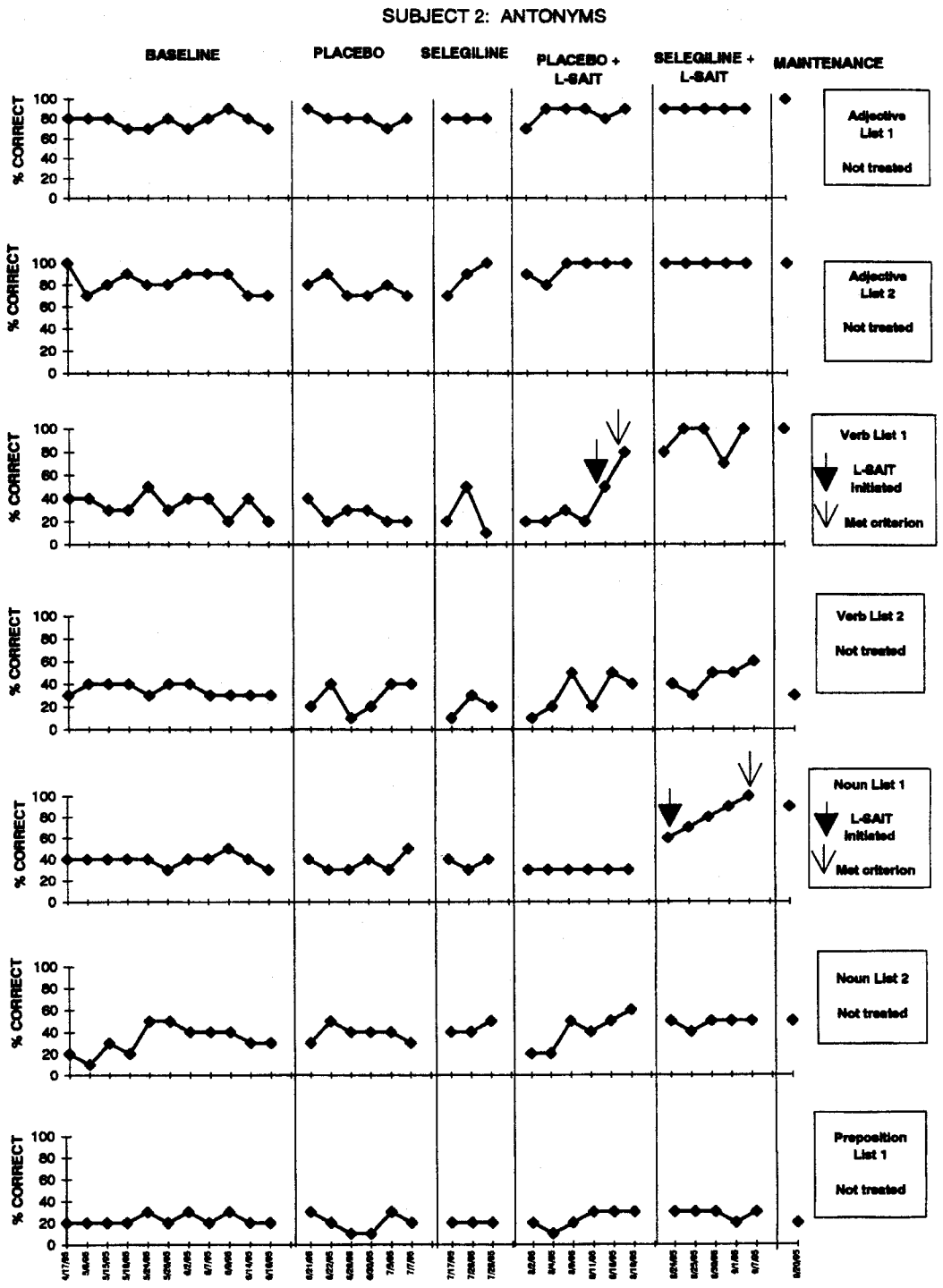

Figure 5. Percentage of correctly produced antonyms for trained and untrained 10-item form class lists across all experimental phases. *Note.* L-SAIT = lexical–semantic activation inhibition therapy.

baseline, placebo, and selegiline phases. As such, during the placebo+L-SAIT phase, verb list 1 was targeted. Inspection of these data reveals an immediate treatment effect with the initiation of L-SAIT and criterion level performance within two subsequent probe sessions. Noun list 1 was targeted during the selegiline+L-SAIT phase. Inspection of these data reveals immediate and linear

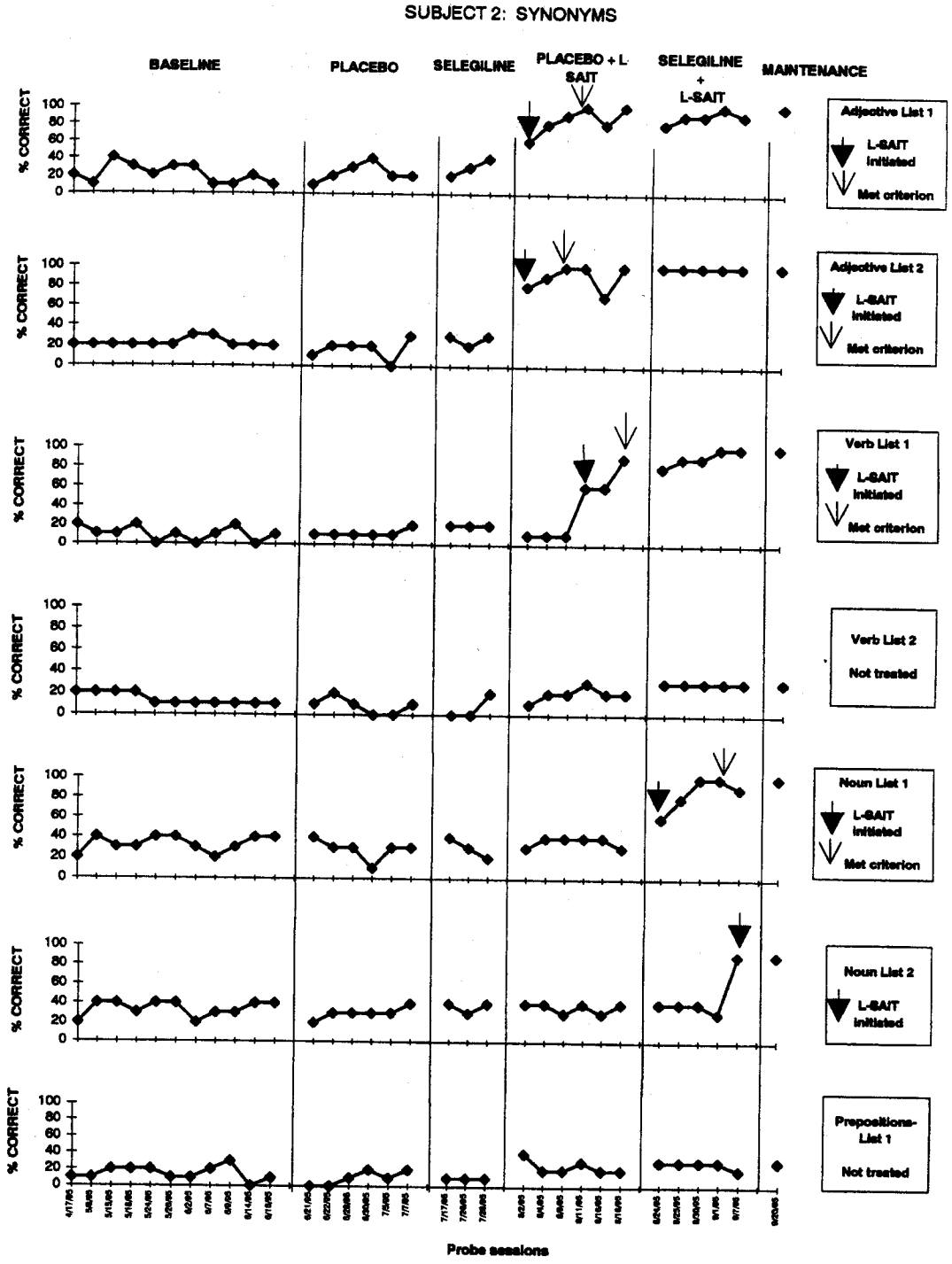

Figure 6. Percentage of correctly produced synonyms for trained and untrained 10-item form class lists across all experimental phases. *Note.* L-SAIT = lexical–semantic activation inhibition therapy.

improvement to criterion level performance within five probe sessions. Generalization of treatment gains to lists within and across form classes was *not* evident. Maintenance of treatment gains for the verb and noun lists *was* demonstrated. In addition, performance did not change relative to baseline levels with the administration of either placebo or selegiline in the absence of L-SAIT.

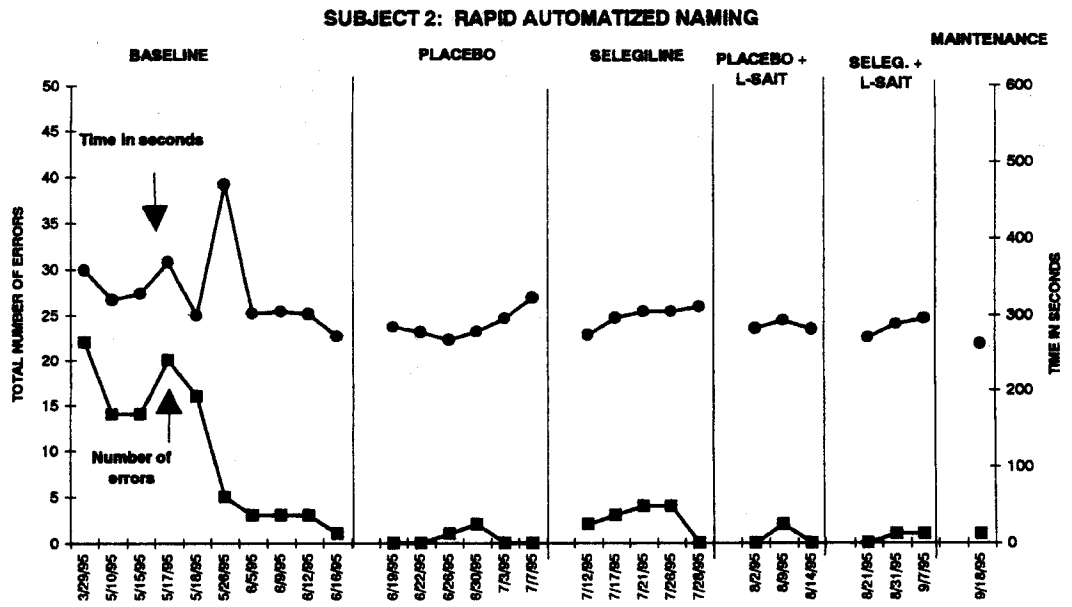

Figure 7. Number of naming errors and the time in seconds to complete the combined subtest of the Rapid Automatized Naming Test (Denckla and Rudel 1976). *Note.* L-SAIT = lexical–semantic activation inhibition therapy.

Synonyms

Figure 6 shows Subject 2's performance on the synonym generation task. As with Subject 1, the synonym task was more difficult than the antonym tasks, resulting in low and relatively stable baselines for most lists. Further, performance did not change substantively relative to baseline levels for any of the word lists with the administration of either placebo or selegiline in the absence of L-SAIT. Adjective lists 1 and 2 were trained concurrently during the placebo + L-SAIT phase. Inspection of these data reveals parallel and improved performance with criterion being met following four and three probe sessions respectively. Verb list 1 was also trained during this phase, and immediate improvement was observed with the initiation of L-SAIT. Criterion level performance was achieved during the sixth probe session. The application of L-SAIT to noun list 1 during the selegiline + L-SAIT phase also yielded immediate and substantive improvement relative to performance during previous experimental phases and criterion was met during the fourth probe session. These was also an immediate treatment effect on noun list 2 during this phase. It is noteworthy that this effect was evident only when L-SAIT was initiated, and was not evident when selegiline was being administered prior to the initiation of L-SAIT. As with the antonym task, generalization of treatment gains to lists within and across form classes was *not* evident. Maintenance of treatment gains *was* evident for all five treated lists.

Rapid Automatized Naming Test

Figure 7 illustrates Subject 2's performance on the combined subtest of the Rapid Automatized Naming (RAN) Test (Denckla and Rudel, 1976) across all phases of the study. Following a rapid acquisition effect during the baseline phase in which error rates decreased from about 23 to 5 and less, time to test completion and error rates did not change across subsequent phases of the study.

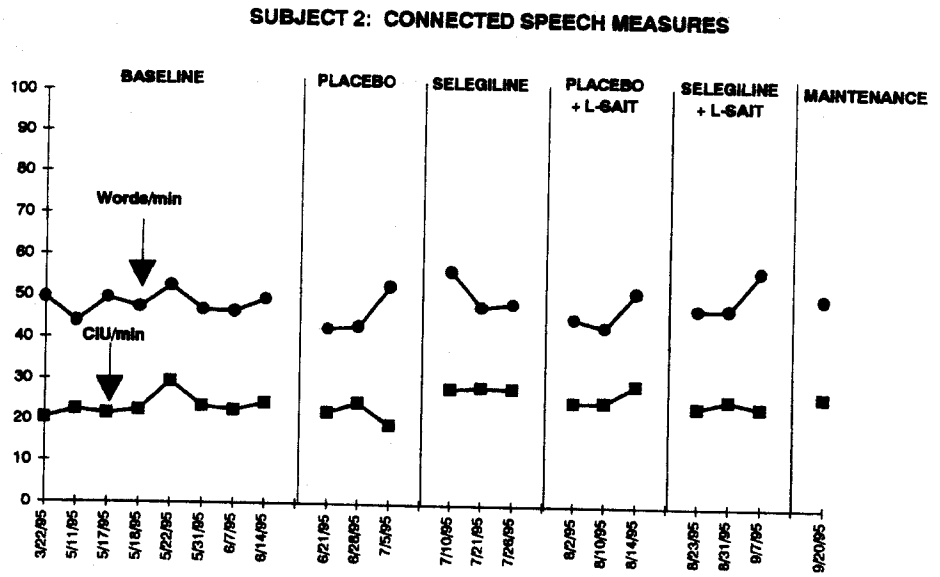

Figure 8. Words per minute and correct information units per minute (CIU/min) derived from samples of connected speech (Nicholas and Brookshire 1993). *Note.* L-SAIT = lexical–semantic activation inhibition therapy.

Information content

Figure 8 represents Subject 2's performance on measures of verbal productivity and informativeness (Nicholas and Brookshire 1993) derived from connected speech samples collected across all experimental phases. As with Subject 1, no change in performance across phases was judged for either metric.

Discussion

This study demonstrated the positive effects of L-SAIT for the retrieval of words for two individuals with stroke-induced aphasia. Although L-SAIT was not administered in the absence of placebo, *d*-amphetamine or selegiline, we conclude that neither the placebo nor the pharmacological agent resulted in a treatment effect. That is, the positive effects are confidently attributed to the L-SAIT treatment alone. This finding generally replicates the results from the McNeil *et al.* (1995) study demonstrating the positive acquisition of naming behaviour with the institution of L-SAIT. Maintenance of treatment effects was evidenced for all treated lists. However, generalization was *not* evidenced for either subject within or across form class, or on connected speech measures. Generalization was evidenced on the RAN, in the form of reduced naming errors without a concomitant reduction in processing speed for Subject 1. Maintenance of the positive acquisition effects was not demonstrated in the earlier treated subject with primary progressive aphasia; however, it was evident in both of the current subjects over the relatively short (approximately 3 weeks) time that it was assessed.

Generalization of acquisition effects was evidenced within and across form classes for the subject with PPA previously reported by McNeil *et al.* (1995). However, no such generalization was evidenced for either of the subjects in the current study. Generalization of L-SAIT treatment (during the placebo + L-SAIT phase) was evidenced in the form of reduced semantic paraphasias on the Rapid

Automatized Naming Test for Subject 1 but not for Subject 2. This generalization effect was maintained across subsequent treatment and non-treatment phases of the study.

In the previous study, only adjectives were targeted for treatment. In the current study, L-SAIT was applied to lists of adjectives, verbs and nouns with positive acquisition and maintenance effects, thus extending the findings from the earlier study. Although this extension is theoretically and practically important, McNeil *et al.* (1995) proposed that the treatment of adjectives should provide the best opportunity for generalization across word classes. Given the lack of generalization within or across word classes, along with the equivalent treatment effects achieved for both of the subjects in this investigation, this hypothesis is certainly weakened.

The acquisition and maintenance effects that were achieved, occurred with 60 or fewer trials for each word in the treatment list. This represents a relatively rapid rate of acquisition. However, once the task was acquired, it does not appear to represent sufficient practice to make the access automatic and thus allow for either the diminution of required processing resources or for the efficient allocation of them. Either or both of these conditions are hypothesized to be necessary for generalization to occur to untrained members within and across form class categories.

The lack of a pharmacological effect in the absence of the behavioural treatment was predicted based upon the paucity of positive findings from the administration of any pharmacological agent alone (e.g. Darley *et al.* 1977). The negative placebo effect was not consistent with the expectations generated from the literature. The fact that there were no differential acquisition or generalization effects between pharmacotherapy (both *d*-amphetamine and selegiline) plus L-SAIT and placebo plus L-SAIT conditions is logically consistent with the findings reported by McNeil *et al.* (1995) for Subject G.P. These investigators reported no differential effects between behavioural intervention alone and behavioural intervention combined with *d*-amphetamine. However, the findings of the current study are not consistent with either the benefits reported from animal studies (Feeney *et al.* 1982, Boycson and Feeney 1984) or from the human studies (Clark and Mankikar 1979, Crisostomo *et al.* 1988) reporting positive effects of supplementing the treatment of motor behaviour with *d*-amphetamine. The results of the current study are also not consistent with the positive effects reported by Walker-Batson *et al.* (1991) using *d*-amphetamine, or with the positive effects reported by several investigators using bromocriptine (Albert *et al.* 1988, Bachman and Morgan 1988, Gupta and Mlcoch 1992). It must be remembered, however, that serious experimental design limitations of all of these studies proscribe their power as predictors. It is our interpretation of the data from this investigation and those of the previous studies using either *d*-amphetamine or bromocriptine either as a sole treatment or as a supplement to a behavioural treatment for aphasia, that there is insufficient justification for their use at this time. This does not imply that the enterprise of exploring pharmacological supplementation to behavioural treatments should not be continued in a systematic way. It does, however, lead to the suggestion that careful experimental designs should be employed to evaluate the effects of pharmacological interventions for aphasia, a situation that has been in short supply to the present.

This negative finding, and the ones that precede it, should also not be interpreted as a suggestion that the relevant experimental variables such as dosage levels have

in any way been explored. The dosage levels used in the present investigation were derived from precedents established by the pharmacological agents effective dosages used for the management of very different neurological disorders and behavioural manifestations, and from the clinical experience and 'best guess' of the physician administering the drug (S. L. S.). A systematic exploration of effective dosages such as those attempted by Gupta and Mlcoch (1991), but with a more appropriate experimental design, is a necessary next step if these pharmacological agents are to be utilized in future studies. It is not time to abandon this line of research. A reasonable neurobiological rationale has been established for the use of catecholamine agonists in recovery of function following stroke. At this time only six subjects have been studied using bromocriptine, and only four subjects have been studied with amphetamines (dextro-amphetamine or selegiline). Although the temptation to accept the null hypothesis may be strong, we must not yield to it. Rather, we must accept the stimulus of the enigmatic and adhere to the principles of scientific rigour that will eventually produce sufficient interpretable data that will serve as the evidence with which to judge the efficacy of pharmacological agents as supplements to aphasia treatment.

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