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# A Double-Blind, Placebo-Controlled Study of the Use of Amphetamine in the Treatment of Aphasia

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*Background and Purpose*—A number of studies suggest that drugs which increase the release of norepinephrine promote recovery when administered late (days to weeks) after brain injury in animals. A small number of clinical studies have investigated the effects of the noradrenergic agonist dextroamphetamine in patients recovering from motor deficits following stroke. To determine whether these findings extend to communication deficits subsequent to stroke, we administered dextroamphetamine, paired with speech/language therapy, to patients with aphasia.

*Methods*—In a prospective, double-blind study, 21 aphasic patients with an acute nonhemorrhagic infarction were randomly assigned to receive either 10 mg dextroamphetamine or a placebo. Patients were entered between days 16 and 45 after onset and were treated on a 3-day/4-day schedule for 10 sessions. Thirty minutes after drug/placebo administration, subjects received a 1-hour session of speech/language therapy. The Porch Index of Communicative Ability was used at baseline, at 1 week off the drug, and at 6 months after onset as the dependent language measure.

*Results*—Although there were no differences between the drug and placebo groups before treatment ($P=0.807$), by 1 week after the 10 drug treatments ended there was a significant difference in gain scores between the groups ($P=0.0153$), with the greater gain in the dextroamphetamine group. The difference was still significant when corrected for initial aphasia severity and age. At the 6-month follow-up, the difference in gain scores between the groups had increased; however, the difference was not significant ($P=0.0482$) after correction for multiple comparisons.

*Conclusions*—Administration of dextroamphetamine paired with 10 1-hour sessions of speech/language therapy facilitated recovery from aphasia in a small group of patients in the subacute period after stroke. Neuromodulation with dextroamphetamine, and perhaps other drugs that increase central nervous system noradrenaline levels, may facilitate recovery when paired with focused behavioral treatment. (*Stroke*. 2001;32:2093-2098.)

**Key Words:** aphasia ■ cerebrovascular disorders ■ dextroamphetamine ■ stroke

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Over the last 2 decades there have been significant advances in knowledge regarding central nervous system plasticity and recovery of function from the basic science laboratory,[1–3] yet there has been little application of this knowledge to rehabilitation methodologies. Recent investigations suggest that both timely training and lesion-induced plasticity are required for amplification of network plasticity.[4] In addition to evidence for plasticity of the adult cortex, a growing body of literature supports the facilitating effects of certain neuropharmacological agents on recovery of function.[5] In animals, norepinephrine in particular has been shown to enhance behavioral recovery when administered in the subacute period after injury.[6]

After experimental cortical lesions, administration of dextroamphetamine (which blocks reuptake and enhances release of norepinephrine) results in improved recovery in motor

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function, sensorimotor integration, and binocular depth perception.[3,7,8] Dextroamphetamine-accelerated behavioral recovery has also been found to correspond to enhanced neural sprouting and synaptogenesis after experimental infarction.[9] The dextroamphetamine-facilitated recovery is greater when drug treatment is paired with practice or training during the drug action period compared with drug administration alone.[3,8,10] The importance of norepinephrine mediation of central nervous system recovery is also supported by the fact that drugs which act as norepinephrine antagonists have reinstated motor deficits in animals[11] and hindered recovery from aphasia in humans.[12] The critical timing window for drug administration to facilitate recovery is not known. In a small number of animals, administration of dextroamphet-

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amine paired with visual experience 90 days after injury did not enhance recovery of binocular depth perception.[8]

We previously reported increased rate (1 week after drug cessation) and extent (6 months' follow-up) of recovery from hemiplegia subsequent to stroke when low-dose dextroamphetamine was paired with physical therapy during the subacute recovery period.[13] In unblinded pilot studies,[14,15] we also found an increased rate of recovery from aphasia when low-dose dextroamphetamine was paired with speech/language therapy. To our knowledge, this is the first report of a double-blind, placebo-controlled study of the effects of dextroamphetamine on recovery from aphasia after stroke. The Porch Index of Communicative Abilities[16] (PICA) was used as the dependent language measure. This measure was chosen because it has been shown to be a highly reliable and sensitive measure of changes in language across time. We sought to determine whether low-dose administration of dextroamphetamine paired with speech/language therapy would increase rate and/or extent of recovery from aphasia.

## Subjects and Methods

Twenty-one subjects (13 men and 8 women) who had a single, left, nonhemorrhagic middle cerebral artery distribution infarction participated in the study. All patients were native English speakers aged 41 to 71 years. Diagnosis was based on neurological and radiological examination. The NIH Stroke Scale (NIHSS)[17] was administered at entry to provide a baseline score of degree of neurological involvement. Either CT or MRI confirmed the presence of a single infarction at entry. Patients' lesions were reconstructed onto templates and entered into a microcomputer with software developed by Frey et al[18] for the calculation of lesion volume. The presence of aphasia was defined as a score of 10 to 70 points on the PICA. Subjects were entered in a consecutive manner using a stratified randomization plan[19] based on severity at baseline and presence or absence of a motor component, ie, hemiplegia, oral apraxia, or apraxia of speech. Severity of aphasia was determined on the overall PICA score; patients with scores $\leq 40$ were classified as having severe aphasia and those with scores between 41 and 70 as having moderate aphasia. This careful subject definition of moderate or severe aphasia was purposely established to control for severity across groups. Exclusion criteria specified that none of the subjects have a terminal medical condition such as AIDS or cancer, other coincident neurological disease, history of psychiatric illness or extensive alcohol or drug abuse, unstable cardiac dysrhythmia or uncontrolled hypertension ($>160/100$ mm HG), or untreated hyperthyroidism. Additionally, subjects could not be receiving $\alpha$-adrenergic antagonists or agonists or be aged $>80$ years. Patients were closely monitored in an attempt to eliminate any confounding medications during the 6-month course of the study.[20] Written informed consent was obtained from all subjects or their legal representatives before the study, and the research protocol was approved by the institutional review boards for human subjects at each of the participating medical centers.

### Procedures

Subjects were recruited over a 4-year period of study funding in which the medical charts of approximately 850 patients were screened. Sample size was projected to be 32 patients. Subjects who met criteria for entry and consented were assigned, in blocks of 4, to either the dextroamphetamine or placebo group by the biostatistician, who used the stratification procedure described by Therneau.[19] All participants, including the research investigators, clinicians, patients, and the patients' primary-care physicians, were blinded to patient assignment to drug or placebo. A baseline PICA aphasia score was obtained 1 to 3 days before study initiation in all subjects.

## Drug Administration and Speech/Language Therapy Treatment

The protocol specified that patients be entered between days 16 and 45 after stroke onset and receive an oral dose of 10 mg dextroamphetamine or placebo paired with speech/language therapy on a 3-day/4-day cycle for 10 sessions over 5 weeks. Thirty minutes after drug/placebo administration, patients started a 1-hour session of individual speech/language therapy. Each patient received equal segments of speech/language treatment in auditory comprehension, speaking, reading, and writing, with the order of treatment rotated each session. The level of treatment was initially determined by the patient's performance on the PICA and thereafter on the previous session's data. The speech language protocol was based on a traditional stimulation/facilitation model with a hierarchy of tasks collated from the published intervention literature.[21,22] Use of the protocol was individualized as needed to treat a patient's specific disabilities. A patient was generally stimulated at 3 levels per modality, starting with the level at which the patient had previously attained 60% to 80% accuracy and continuing up to the highest level at which an approximate response could be obtained. Our decisions regarding task difficulty have been influenced by animal studies which suggest that brain plasticity is use dependent[23,24] and that the type of input is important. We strove for a balance between establishing an infrastructure for communication and stimulating the most complex language behaviors possible. It should be noted that because we study hemiplegia as well as aphasia, some patients also participated in physical therapy treatment. We tightly scheduled the speech/language and physical therapy to occur during the active drug period, with speech therapy always administered first. Predrug and postdrug measures of heart rate and blood pressure were documented in each session. The number of hours of direct speech/language therapy in addition to the dextroamphetamine treatment protocol was also documented.

## Data Preparation

The dependent measure was the PICA. This highly reliable test has 18 subtests in the modalities of verbal, graphic, reading, and gesture, which yield an overall score expressed as a percentile. PICA overall scores were obtained at baseline, 7 days after drug sessions stopped, and again at 6 months after stroke onset for comparison between the 2 groups. For conservative comparisons between the 2 groups, we used the Bonferroni correction. In addition, we defined a 15 percentile point gain, as suggested previously by Wertz et al,[25] as a significant clinical difference to determine clinical change at the 1-week-off-drug assessment. Two experienced PICA administrators independently scored 20% of video taped assessments and reached 100% agreement on a point-by-point basis. Data analyses were performed with SAS, release 6.12 (SAS Institute Inc).

## Results

Twenty-five subjects were recruited to the study over the 4-year study period. Four subjects did not complete the study. Two were discharged during the treatment phase, 1 for nonattendance and the other for uncontrolled hypertension. One subject exhibited cognitive deficits and was discharged from the study, and 1 subject (S24 in the dextroamphetamine group) moved out of the country and could not be assessed at 6 months. The most frequently occurring reasons for patient exclusion were evidence of hemorrhagic or brain stem stroke, previous cerebral lesion with residual deficit, mild aphasia deficit, multiple medical problems, other coexisting neurological conditions, and age. Although these exclusions made recruitment difficult and no doubt accounted for the projected sample size of 32 not being achieved, we believe that this subject exclusion is essential for an initial efficacy study of this type.

| Baseline Characteristic | Placebo | Dextroamphetamine | P |
|---|---|---|---|
| Days after onset, n | 29.3 | 31.3 | 0.3838* |
| Sex (M/F) | 7/2 | 6/6 | 0.3670† |
| Age, y | 61.3 | 51.8 | 0.0637* |
| NIHSS score | 9.9 | 10.6 | 0.1573* |
| Baseline PICA overall score | 35.3 | 33.5 | 0.8070* |

Values (except sex) are mean.

*By 2-sample *t* test and †Fisher exact test.

Twelve subjects received dextroamphetamine and 9 received placebo. Comparisons of day of study initiation, gender, age, and baseline NIHSS and PICA overall scores revealed no significant differences between the groups (Table 1). Lesion volumes did not differ between the 2 treatment groups. Within-session monitoring of heart rate and blood pressure revealed no significant fluctuations due to drug administration. In addition, at no time during the 6-month course of the study was there documentation of any negative event that could be attributed to dextroamphetamine administration.

Table 2 shows individual baseline PICA overall scores with gain scores as well as aphasia type and hours of total speech language treatment, including the 10 drug/placebo sessions for the 2 groups across the study period. (Subjects are numbered consecutively whether they participated in the motor or language aspects of the protocol). Table 3 shows mean PICA overall percentile changes at the 1-week-off drug assessment and the 6-month follow-up and the number of treatment hours at 1 week off drug.

While there were no differences between drug and placebo groups before treatment ($P=0.807$), by 1 week after the conclusion of the 10 drug/placebo sessions there was a significant difference in gain scores between the groups ($P=0.0153$), with the greater gain in the dextroamphetamine group. The difference ($P=0.0106$) was still significant when corrected for initial aphasia severity ($P=0.0974$) and age ($P=0.2771$). Additionally, at the 1-week-off-drug assessment, which was poststroke day 73 for the dextroamphetamine group and day 71 for the placebo group, 83% (10 of

**TABLE 2.   Individual PICA Overall Scores With Gain Scores at 1 Week After Treatment and 6-Month Follow-Up Plus Number of Hours of Speech/Language Therapy**

| Subject No./Aphasia Classification | Baseline Aphasia Score (PICA) | 1 Week Off Drug | | Hours of Treatment, n | 6-Month Follow-Up | | Total Hours of Speech Therapy (6 mo), n |
|---|---|---|---|---|---|---|---|
| | | Score | Gain Score | | Score | Gain Score | |
| Placebo (n=9) | | | | | | | |
| S1/Broca+ | 17.0 | 27.0 | 10.0 | 24.0 | 35.0 | 18.0 | 38.0 |
| S2/Anomic | 47.0 | 66.0 | 19.0 | 20.0 | 78.0 | 31.0 | 20.0 |
| S9/Wernicke | 23.0 | 38.0 | 15.0 | 40.0 | 43.0 | 20.0 | 81.0 |
| S14/Wernicke | 33.0 | 36.0 | 3.0 | 28.0 | 38.0 | 5.0 | 45.0 |
| S23/Wernicke | 25.0 | 34.0 | 9.0 | 15.0 | 37.0 | 12.0 | 27.0 |
| S25/Broca | 20.0 | 29.0 | 9.0 | 25.0 | 31.0 | 11.0 | 52.5 |
| S28/Anomic | 58.0 | 72.0 | 14.0 | 15.0 | 78.0 | 20.0 | 21.0 |
| S29/Broca+ | 41.0 | 54.0 | 13.0 | 42.0 | 68.0 | 27.0 | 111.0 |
| S30/Wernicke | 54.0 | 64.0 | 10.0 | 36.0 | 69.0 | 15.0 | 68.0 |
| Mean | 35.3 | 46.7 | 11.3 | 27.2 | 53.0 | 17.7 | 51.5 |
| Dextroamphetamine (n=12) | | | | | | | |
| S3/Broca+ | 19.0 | 36.0 | 17.0 | 22.5 | 38.0 | 19.0 | 43.5 |
| S4/Broca+ | 30.0 | 49.0 | 19.0 | 25.0 | 58.0 | 28.0 | 65.0 |
| S6/Broca+ | 47.0 | 67.0 | 20.0 | 56.0 | 75.0 | 28.0 | 98.0 |
| S7/Global+ | 8.0 | 25.0 | 17.0 | 70.0 | 46.0 | 38.0 | 100.0 |
| S11/Wernicke | 32.0 | 43.0 | 11.0 | 60.0 | 62.0 | 30.0 | 72.0 |
| S13/Broca | 27.0 | 43.0 | 16.0 | 38.0 | 48.0 | 21.0 | 71.0 |
| S24/Broca | 50.0 | 71.0 | 21.0 | 20.0 | NA | NA | NA |
| S26/Broca+ | 13.0 | 19.0 | 6.0 | 20.0 | 23.0 | 10.0 | 50.0 |
| S27/Global+ | 18.0 | 34.0 | 16.0 | 23.0 | 39.0 | 21.0 | 53.0 |
| S32/Conduction | 69.0 | 87.0 | 18.0 | 20.0 | 92.0 | 23.0 | 59.0 |
| S33/Conduction | 33.0 | 55.0 | 22.0 | 18.0 | 66.0 | 33.0 | 41.0 |
| S35/Anomic | 56.0 | 73.0 | 17.0 | 29.0 | 82.0 | 26.0 | 75.0 |
| Mean | 33.5 | 50.2 | 16.7 | 33.0 | 57.2 | 25.2 | 66.0 |

+ indicates severe or profound apraxia of speech.

**TABLE 3.  Main Results**

|  | Placebo | Dextroamphetamine | P |
|---|---|---|---|
| PICA overall mean gain score at 1 week off drug | 11.3 | 16.7 | 0.0153* |
| Achieved PICA 15 percentile point change at 1 week off drug | 22% | 83% | 0.0092† |
| PICA overall mean gain score at 6-month follow-up | 17.7 | 25.2 | 0.0482* (NS) |
| Mean speech/language therapy hours at 1 week off drug | 27.22 | 33.45 | 0.3331* |

*By 2-sample *t* test (Bonferroni adjustment, $\alpha=0.025$) and †Fisher exact test.

12) of the dextroamphetamine subjects compared with 22% (2 of 9) of the placebo subjects had surpassed the 15 points that we had defined as a clinically significant change ($P=0.0092$, Fisher exact test). At the 6-month follow-up, the difference in gain scores between the groups was maintained and even increased; however, the difference was not significant ($P=0.0482$) after correction for multiple comparisons. There was no significant difference in the number of hours of speech/language therapy both within and outside of the drug/placebo sessions at the 1-week-off-drug assessment or at the 6-month follow-up between the 2 groups. The Figure plots the differences in PICA overall gain scores between the 2 groups at the 1-week-off-drug assessment and the 6-month follow-up.

The stratification plan appeared to be successful in allotting equally severe patients in the dextroamphetamine and placebo groups with a range of severity in terms of baseline overall PICA scores. It should be noted that this particular sample had a large number of patients with severe aphasia at baseline. In the dextroamphetamine group, 6 of 12 patients had baseline PICA scores of ≤30. In the placebo group, 4 of 9 subjects had baseline PICA scores of ≤30. In addition, at baseline there were 6 subjects in the dextroamphetamine
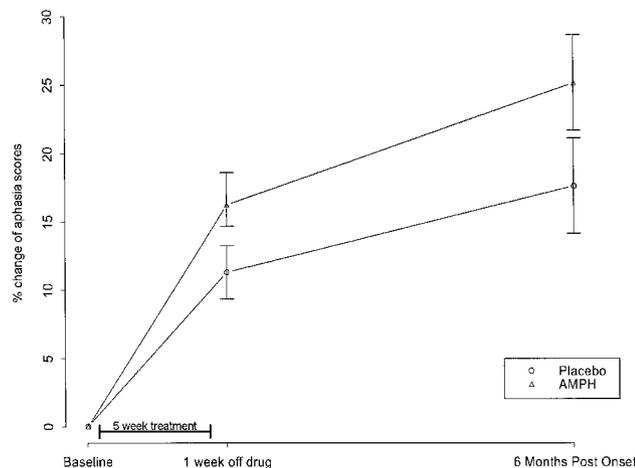


Mean±SEM percentile change in overall PICA scores at the 1-week-off-drug assessment and the 6-month (after stroke onset) follow-up for the dextroamphetamine [AMPH] and placebo groups. The 1-week-off-drug data point was taken 1 week after the last of 10 treatment sessions given at 3- or 4-day intervals over a 5-week period. Treatment was initiated between 16 and 45 days after stroke onset.

group who showed profound or severe apraxia of speech and 2 subjects in the placebo group who had severe apraxia of speech (see Table 2).

## Discussion

In this study of 21 subjects with moderate to severe aphasia deficits, administration of dextroamphetamine paired with speech/language treatment during the subacute recovery period accelerated the rate of aphasia recovery, as assessed by a reliable test of communication ability.[16] One week after drug sessions ended, there was a significant difference in recovery between the groups. There was also a significant difference in the number of subjects who achieved the predetermined clinical change score of 15 points. The 16.7-point change in PICA overall score in the dextroamphetamine group with only 10 drug treatment sessions and 33 total hours of language therapy over the 5-week study period compares favorably with previous aphasia efficacy studies that used the PICA as the primary outcome measure at a similar period of study entry.[25] Subjects in the Veteran's Administration Cooperative Study, who were also entered in the subacute recovery period, made an 18.2-point PICA overall change after being treated over 12 weeks and receiving between 96 and 120 hours of treatment.[25] These results confirm previous clinical work by ourselves[12–14] and others[26,27] of a facilitative effect of dextroamphetamine on rate of behavioral recovery after occlusive stroke.

It cannot be determined from the present study whether recovery endures after drug treatment. Although at the 6-month follow-up the numerical difference in gain scores between the groups increased, the difference was not significant when corrected for multiple comparisons. In this study we purposely chose a conservative approach to the data analysis. However, incorporating this adjustment increases the risk of not detecting an effect when an effect actually exists. The power of this study to detect differences is also limited because the sample size was smaller than projected.

The results of this study extend previous clinical findings in motor recovery to recovery from aphasia and suggest that the dextroamphetamine effect found in animal models of stroke recovery has application to human rehabilitation. When we consider the rather moderate effects of the low dose of dextroamphetamine used in this protocol in severely aphasic subjects over 10 paced dextroamphetamine sessions with 33 hours of speech/language therapy, we have to ask what more drug and more treatment might do. It is also

noteworthy that patients enrolled into this dextroamphetamine protocol suffered no adverse reactions, a finding that we have previously reported.[28]

This study is limited because of the small group of aphasic subjects and may not represent all stroke patients. However, because many of the patients we studied had severe aphasic deficits at entry, effects in this small sample would appear to be meaningful. Additionally, from this small sample it is not possible to specify whether aphasia type predicts response. In this particular group of aphasic patients, day of study initiation (up to day 45) did not determine response or nonresponse. It should be noted that this treatment is not equally effective for all deficits, a finding also observed in the animal model.[29] Patients with an initial apraxia of speech so severe that they had no speech output did not recover verbal ability as a means of communication, although other language areas such as writing were significantly enhanced. Larger samples to allow for greater stratification in terms of severity, types of aphasia, and age would better characterize response or nonresponse.

## Acknowledgments

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# Editorial Comment

# Changing Foundations of Speech Therapy

The occasional shifts of scientific thought may appear capricious. The foundation for some changes are likely difficult to observe and perhaps impossible to understand. Others may be straightforward. Broca's report of a few cases of aphasia had remarkable consequences, initiating the study of brain function. While there had been descriptions of language deficits associated with left hemisphere lesions, they were not generally accepted. The idea of the cortex "acting as a whole" was the dominant interpretation of cortical organization. Broca's conclusion, that the third frontal convolution was the

critical center for the "faculty for articulate language," required a change to localization of function in cortex. According to Henry Head, "These communications produced the greatest excitement in the medical world of Paris."[1]

Recently, a marked change of expectations regarding the potential of neurorehabilitation changed from pessimism to enthusiasm regarding both physical therapy (PT) and speech therapy (ST). In part this reflects the later times post-injury when experimental interventions are reportedly effective. Also, the acceptance by the rehabilitation team that laboratory work using animals may have implications for the treatment of aphasia represents a major change in attitude. The series of studies[2] by the Dallas group, Walker-Batson and her colleagues, began by extending laboratory findings that recovery from hemiplegia can be enhanced to a higher outcome level by combining noradrenergic agonists with PT in rat or cat.[2] This combination approach has been described as a "new frontier"[3] that "holds considerable promise."[4] The use of pharmacotherapy as an adjunct to PT and ST is not new. Earlier investigations, including Sciclounoff in 1934 and Luria in the 1940s, described the efficacy on outcome of cholinergic drugs combined with PT and ST (reviewed in Reference 5).

While the study of the relation between aphasia and areas of cortical injury originated over a century ago, the attempted treatment of aphasia has a surprisingly short history. The study considered the first investigation of "treatment efficacy" in ST used a no-treatment control group and was published in 1964 (discussed in Reference 6 [page 31]). Unlike other health care specialties, ST was founded on educational principles, "the aphasic patient was to be taught language just as a child is taught."[6] Only in the 1970s were outcome studies begun and reviews of the few controlled experiments describe the results as "unimpressive."[7] The recent review and analysis by the Cochran group[8] of the controlled studies on the efficacy of ST summarized this outcome literature as "not been shown either to be clearly effective or clearly ineffective." Given this background, the studies by Walker-Batson and colleagues are unique compared to those typically conducted on the efficacy of rehabilitation treatments a decade earlier.

The biomedical sciences increasingly recognize the need for statistical analysis to determine the possibility that an observed difference was due to chance. The use of multiple measurements presents the opposite problem: Conduct enough significance tests and some will be significant by chance.[9] The Bonferroni correction is one of several methods used to maintain the alpha level at 0.05 when multiple significance tests are conducted. By consensus, the alpha level is set at 0.05, accepting the risk of 1 in 20 that statistical tests may give a "significant" difference by chance. If 5 tests are computed, the chance of 1 being significant due to chance is 0.20. Using the Bonferroni correction, the alpha level of each individual test is adjusted downward to ensure that the overall risk for a number of tests remains at 0.05. A problem results from collecting multiple measures, as the adjustment of the alpha level will make it more difficult to reach

significance. The Bonferroni correction has been the subject of considerable controversy.[9,10] An important problem is the absence of consistency in the use of such adjustments within the same journal and for similar studies. To illustrate this inconsistency, compare the current study by Walker-Batson et al to the quite similar study of the effect of piracetam on aphasia recovery published in *Stroke*.[11] The current study required only *t* tests to compare 2 groups at 2 time points; however, a reviewer requested the use of the Bonferroni to adjust the alpha level. The piracetam study[11] included calculation of more than 17 significance tests of the aphasia and neuropsychological tests, and they do not report any alpha level adjustment. The study also included significance tests of treatment-induced rCBF changes measured by PET scans. How to adjust for multiple comparisons in such measures and how these significance tests should be counted when adjusting the alpha level requires a separate discussion. I am not suggesting that alpha-level adjustments using the Bonferroni or other methods are appropriate; rather, *Stroke* should take a lead and adopt a consistent policy on these issues.

The major difficulty in conducting studies such as this by Walker-Batson et al is often not appreciated. To locate, test, and follow up the 21 subjects used in this study required 4 years of patient recruitment. As noted in a review of ST efficacy,[6] patient recruitment is a general problem for these studies and helps explain why so few studies are conducted. For some areas within neuroscience, after 4 years the original hypothesis may no longer be of any interest.

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