*Pilot Study*

# Aerobic Exercise as an Adjuvant to Aphasia Therapy: Theory, Preliminary Findings, and Future Directions

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## ABSTRACT

**Purpose:** This study investigated whether participation in aerobic exercise enhances the effects of aphasia therapy, and the degree to which basal serum brain-derived neurotropic factor (BDNF) concentrations fluctuate after the beginning of aerobic exercise or stretching activities in individuals with poststroke aphasia.

**Methods:** The study used a single-subject, multiple-baseline design. Seven individuals with chronic poststroke aphasia participated in 2 Blocks of aphasia therapy: aphasia therapy alone (Block 1), followed by aphasia therapy with the addition of aerobic activity via bicycle ergometer (n = 5) or stretching (n = 2) (Block 2). Serum BDNF concentrations from blood draws were analyzed in 4 participants who exercised and in 1 participant who stretched.

**Findings:** Three of the five exercise participants demonstrated larger *Tau-U* effects when aphasia therapy was paired with aerobic exercise, whereas 1 of the 2 stretching participants demonstrated a larger effect size when aphasia therapy was paired with stretching. Group-level comparisons revealed a greater overall increase in effect size in the aerobic exercise group, as indicated by differences in *Tau-U* weighted means. BDNF data showed that all 4 exercise participants demonstrated a decrease in BDNF concentrations during the first 6 weeks of exercise and an increase in BDNF levels near or at baseline during the last 6 weeks of exercise. The stretching participant did not show the same pattern.

**Implications:** Additional research is needed to understand the mechanism of effect and to identify the factors that mediate response to exercise interventions, specifically the optimal dose of exercise and timing of language intervention with exercise. ClinicalTrials.gov identifier: NCT01113879. (*Clin Ther.* 2018;40:35–48) 

**Key words:** aphasia, BDNF, exercise, therapy.

## INTRODUCTION

The cognitive benefits of exercise have long been studied in healthy adult populations. More recently, investigations of exercise effects in animal and human models of stroke have begun to contribute to our understanding of the potential for exercise to enhance recovery. For example, aerobic activity has been shown to improve motor recovery after stroke. Findings from studies have shown that aerobic exercise yields improved learning on a reaching task in rats with hemiparesis[1] and better performance on upper

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extremity function measures in humans with hemiparesis.[2] Importantly, reviews suggest that cognitive abilities after stroke may also improve with exercise.[3,4] Indeed, recent studies have demonstrated a positive effect of exercise on executive function,[5,6] speed of information processing,[7] memory,[5,8] and even language.[8] These results are promising and highlight the need for more research investigating the use of exercise for improving cognitive function in individuals with chronic history.

*Aphasia* is a language disorder that can occur after a brain injury, such as a cerebrovascular accident. Aphasia can affect both the comprehension and production of language. It is well established that persons with aphasia (PWAs) after stroke also demonstrate nonlinguistic cognitive impairments.[9] Executive dysfunction often co-occurs with language impairment in part due to overlapping brain regions that support these processes.[10,11] Indeed, studies of the predictors of response to aphasia treatment have demonstrated that nonlinguistic cognitive abilities are related to success in naming therapy.[12–16] This observation suggests that PWAs with other cognitive deficits may be less likely to acquire and maintain therapeutic benefit from naming treatment without an approach that also aims to improve cognitive functions. As language and other cognitive functions are supported by overlapping brain regions, the functions of which have been shown to improve with long-term exercise,[17] there is support for considering long-term exercise as an adjuvant to aphasia treatment.

The mechanism by which aerobic exercise improves cognition and language is also an important component of understanding the potential of exercise-based approaches to aphasia rehabilitation. Findings from studies in animals have shown that the mechanisms by which exercise enhances cognitive functions are closely linked to those of exercise-induced increases in brain-derived neurotrophic factor (BDNF).[18,19] BDNF regulates neuroplasticity molecules, including cyclic AMP response element-binding protein and synapsin-1, which play a role in synapse formation, axonal elongation, and maintenance of the presynaptic structure.[18,20,21] We hypothesize that these synaptic changes may strengthen the connections in the brain, thereby resulting in faster and more efficient processing of information.

However, the findings from studies of the mechanisms underlying aerobic exercise effects in non–neurologically impaired humans have not been straightforward. Zoladz et al[22] found that, in active young men, after 5 weeks of moderate-intensity endurance training, resting BDNF levels (basal levels) were increased, and that BDNF levels were increased immediately after single bouts of exercise that composed the 5-week training (end-exercise levels). However, Schiffer et al[23] compared the effects of moderate-intensity endurance training and moderate-intensity strength training on plasma concentrations of BDNF and insulin-like growth factor-1 in healthy young adults, and found no corresponding changes in either. Studies of the mechanism underlying acute effects of exercise on word learning have also yielded mixed results. For example, Winter et al[24] demonstrated that increased BDNF levels were associated with better short-term learning success in healthy young athletes; however, other studies have not found a relationship between BDNF levels and new word learning.[25,26] Multiple factors influence the relationship between exercise, learning, and BDNF increases, including exercise timing,[26] exercise intensity,[27] and when BDNF levels are measured relative to exercise.[28] The present study investigated potential shifts in basal BDNF levels over time, but did not investigate the acute effects of individual exercise events.

The purposes of the present study was twofold: (1) to determine whether participation in aerobic exercise enhances the effects of aphasia therapy; and (2) to investigate the degree to which basal serum BDNF concentrations fluctuate after the beginning of aerobic exercise or stretching activities in individuals with chronic stroke.

## PATIENTS AND METHODS

### Design

The study used a single-subject, multiple-baseline design across behaviors. Following assessment and baseline procedures, participants completed 2 therapy periods: Block 1 was aphasia therapy alone, and Block 2 was aphasia therapy plus aerobic exercise or stretching. Individuals were reassessed 3 months following the completion of treatment for the investigation of whether gains acquired during treatment were maintained. Two certified speech–language pathologists administered all language therapy and assessments. The study was approved by the institutional review board at the University of Florida (Gainesville, Florida), and participants provided written informed

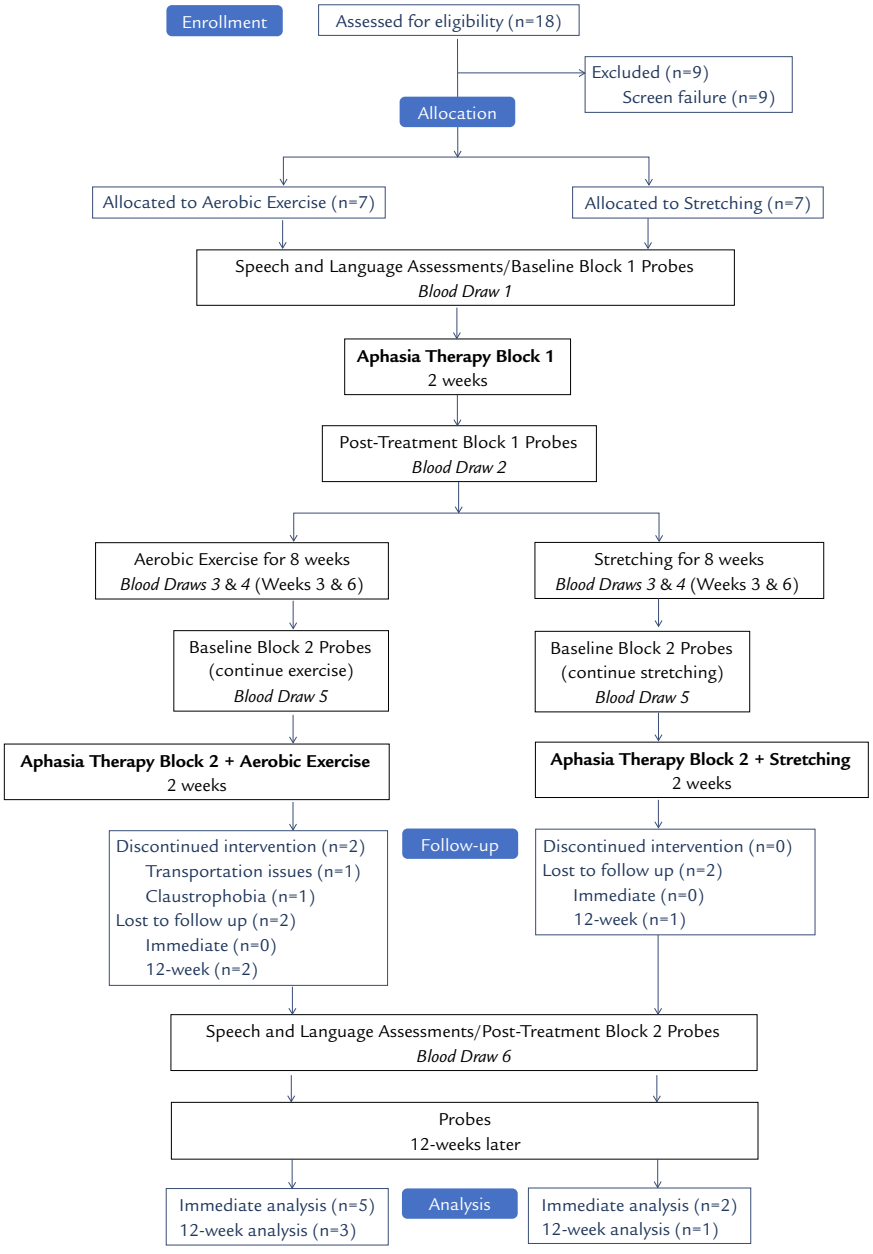


Figure 1. Study design, presented as a flowchart to illustrate the activities that occurred over time.

consent before engaging in study procedures. See Figure 1 for the CONSORT flow diagram.

## Participants

Eighteen individuals were recruited to participate in the study across 2 study sites. Nine individuals met the inclusion criteria and were enrolled in the study, and 7 participants completed the study. One individual dropped out due to transportation issues and the other because of claustrophobia associated with a functional magnetic resonance imaging component that was used in another leg of the study. Given the limited size of the participant pool from which we were recruiting, we decided to assign the first 5 participants to the aerobic exercise group to ensure enough participants for the determination of patterns of response to the treatment. The last 2 participants enrolled were assigned to the stretching group. Inclusion/exclusion criteria ensured

that participants were premorbidly right-handed, native English speaking, ≥6 months poststroke, and had significant anomia as indicated by a raw score of 3 to 46 on the Boston Naming Test.[29] Eligible patients also demonstrated at least minimally intact auditory–verbal comprehension by achieving a score of no less than 2 SDs below normal values on the Auditory Verbal section of the Western Aphasia Battery.[30] Based on medical records and interview of each participant and a close family member, eligible participants did not have evidence of diffuse brain injury or disease. All eligible participants also passed a bicycle ergometry assessment of exercise tolerance[31] that provided estimates of heart rate reserve for aerobic activity (in those participants assigned to the exercise group). Individuals who routinely performed 20 minutes or more of cardiovascular exercise 3 times a week were excluded.

## Assessment, Baseline Naming, and Naming Probes

Standardized speech and language assessments were administered, including the Boston Naming Test[29] and the Western Aphasia Battery.[30] Demographic and assessment data are presented in Table I. During baseline naming, a corpus of 575 pictures was administered twice to develop stimulus sets for the cued picture-naming treatment (CPNT; described in detail in work by Harnish et al[13,32]). Eighty pictures that were named incorrectly on both occasions were selected for training (40 in each Block of therapy) in addition to 20 pictures that were named correctly (10 in each Block of therapy). The latter items were included to reduce frustration associated with repeated attempts at naming difficult items. Thus, 50 unique pictures were selected for naming during each Block of therapy. Baseline naming sessions occurred in 9 to 12 sessions or until a stable baseline was achieved using the *c* statistic[33] prior to each treatment Block. We calculated the *c* statistic based on a composite list of trained and untrained probe items. When we separated these lists, we noted that 2 participants (E1 and S1) showed an ascending trend for trained items prior to initiating therapy. Therefore, to mitigate the effect of an unstable baseline, we calculated effect sizes using *Tau-U*, which corrects for trend in the baseline Block.

Picture-naming probes were administered during baseline sessions, prior to each treatment session, and 3 times after each Block of therapy. Sixty probe items were used for the probe list: a random sample of 20 trained items from period 1, 20 trained items from Block 2, and 20 untrained items. Trained and untrained items were matched for word frequency, living versus nonliving items, number of syllables, and nonoverlapping semantic categories. Participants were given 12 seconds to name probes, which were scored as correct or incorrect by the therapist. Fifteen percent of the picture-naming probe sessions were watched via video recordings and rescored by the treating therapist and a speech–language pathologist uninvolved with the study to calculate intra- and inter-rater reliability.

## Treatment Procedures

### *Block 1*

CPNT[13,32] was delivered by a clinician using a laptop computer with Eprime 1.0 software (Psychology Tools; www.pstnet.com). Participants attempted to

Table I. Demographic and standardized assessment data.

| Participant* | Sex | Age, y | Years of Education | Years Poststroke | BNT | WAB AQ | WAB Classification |
|---|---|---|---|---|---|---|---|
| E1 | Female | 45 | 14 | 7 | 23 | 52 | Broca |
| E2 | Female | 65 | 18 | 3 | 11 | 55 | Conduction |
| E3 | Male | 80 | 14 | 2 | 43 | 80.7 | Anomic |
| E4 | Male | 61 | 15 | 11 | 10 | 43.5 | Wernicke |
| E5 | Female | 65 | 18 | 3 | 33 | 74 | Transcortical motor |
| S1 | Female | 52 | 12 | 5 | 39 | 84.4 | Anomic |
| S2 | Female | 37 | 16 | 2 | 4 | 35.8 | Broca |

AQ = aphasia quotient; BNT = Boston Naming Test[29]; WAB = Western Aphasia Battery.[30]
*Participants E1 to E5 exercised on a bicycle ergometer; participants S1 and S2 stretched.

name 50 pictures. Each picture was presented 8 consecutive times, with a phonemic, semantic, orthographic, or repetition cue provided by the therapist on each trial. CPNT was delivered 4 d/wk for 2 weeks, for ~1 hour or as long as it took to complete all naming trials. All 50 treatment items were presented in random order. The therapist provided encouragement and feedback during the treatment naming attempts.

### *Block 2*

Following Block 1, 5 participants began aerobic exercise and 2 control participants began stretching, 3 d/wk for 8 weeks, each monitored by trained study personnel and supervised by a licensed physical therapist. Aerobic exercise has been shown to increase BDNF in the circulation as well as in specific brain regions.[18] Given these effects, as well as the potential benefits of this type of exercise on the sequelae following stroke, we chose to deliver an aerobic exercise paradigm to our participants. Block 2 of therapy was the same as Block 1, with the exception of training a different set of words. Untrained and infrequently probed items remained the same. Research in animals indicates that training that occurs immediately after exercise can improve rehabilitation, presumably because of the immediate increase in serum BDNF concentrations after exercise[34]; however, it is unknown whether exercise-induced fatigue in the poststroke population may counteract the beneficial effects of exercise if training were initiated immediately after exercise. This phenomenon has been observed anecdotally in inpatient rehabilitation settings in which patients may become so fatigued after physical therapy that they need to rest prior to aphasia therapy. Therefore, in Block 2 we counterbalanced the number of days that individuals participated in aphasia therapy alone and days they participated in aphasia therapy immediately following exercise or stretching as a compromise between potentially positive and negative acute effects of exercise on language behavior during therapy. For example, individuals may have participated in exercise/stretching on Monday, Wednesday, and Friday and aphasia therapy on Monday, Tuesday, Wednesday, and Thursday. Thus, they would have participated in aphasia therapy following exercise on 2 days and aphasia therapy alone on 2 days.

The aerobic exercise protocol began with 10 minutes of warm-up on a bicycle ergometer, 30 minutes of cycling, and 10 minutes of cool-down. Participants exercised for 50 minutes, 3 d/wk for 12 weeks (36 sessions). This exercise duration was chosen based on a report of cognitive and motor changes after 24 sessions of aerobic activity that occurred for 35 minutes per session, plus 5 minutes of ramp-up and cool-down.[7] To target improvements in aerobic capacity, workload on the bike progressed from 50% heart rate reserve in week 1 to 70% heart rate reserve beginning in week 3 and continuing throughout the remainder of the exercise sessions, with bout duration as tolerated (ratings of perceived exertion $<18$)[35] to achieve 30 minutes of cycling. Participants were monitored during training for tolerability, and to track heart rate and blood pressure to ensure sufficient exercise intensity. The stretching protocol was low intensity and not expected to increase heart rate enough to be considered aerobic. There were no adverse effects of the exercise in the present sample. There were no instances of participant fatigue to the extent that they could not participate in aphasia therapy.

## BDNF Sample Collection and Analysis

A 10-mL blood sample was collected by a certified phlebotomist from the antecubital vein of each participant 6 times to establish baseline BDNF levels and fluctuations over time. Samples were collected in 10-mL Vacutainer Venus Blood Serum Separation Tubes (BD Biosciences, San Jose, California). One sample was collected the week prior to Block 1 and the week after Block 1, which were 3 weeks apart. Thus, 2 samples were collected prior to the beginning of exercise/stretching. The remaining 4 samples were collected every 3 weeks, or after every 9 exercise or stretching sessions. This study was designed to investigate possible increases in basal BDNF with exercise. Because evidence suggests an immediate increase in BDNF concentrations in response to acute exercise,[36] no samples were collected following exercise or stretching on the same day. Samples were collected either on days that individuals did not participate in exercise or stretching, or before they began exercise or stretching for the day. That is, because BDNF samples were not designed to measure the acute effects of individual aerobic exercise episodes, they were not collected after exercise. Rather, they were collected at times at which we did not expect to see an acute increase, in order to capture possible basal BDNF shifts.

After collection, samples were gently inverted to mix the clotting agent. Samples remained upright for

30 minutes and were then centrifuged at 1100*g* for 10 minutes at a temperature of 21°C. Serum was extracted using a pipette and deposited into 1-mL tubes. Tubes were individually labeled, entered into a study log, and stored in a freezer at −80°C. Complete BDNF datasets from 5 of the 7 participants from both study sites were available for analysis that are presented here. All samples from E1, E2, and E3 were analyzed at 1 site using a Human Free BDNF Quantikine ELISA kit (R&D Systems, Minneapolis, Minnesota) and samples from E5 and S2 were analyzed at a second site using a Mature BDNF Rapid ELISA Kit (Biosensis, Thebarton, SA, Australia). Thus, all samples in any given participant were analyzed using the same assay kit. However, due to potential variability between ELISA kits, we caution against comparisons across participants that were analyzed at different sites. Standard procedures, per the assay instruction manuals, were followed. Each sample was assayed in duplicate and means calculated to obtain a mean serum BDNF concentration.

### Follow-up Assessment

The protocol included an assessment of all probe items 12 weeks after the completion of the second period of therapy. Because Block 2 of therapy occurred closer in time to the follow-up assessment, we did not compare maintenance between Block. However, we included the follow-up probe scores on the treatment graphs in Figure 2 (see also Supplemental Appendices in the online version at https://doi.org/10.1016/j.clinthera.2017.12.002) in participants who returned to complete the assessment, to illustrate maintenance of items trained in CPNT.

### Statistical Analysis

#### *Effect Size*

Effect size calculations were included as a quantitative index of meaningful change. *Tau-U* was selected because of its advantages over other effect size calculations in that it addresses problematic baseline trend issues, maintains nonoverlap in the evaluation of treatment effects, and is robust enough for small datasets.[37] In the present analyses, any baseline trends over 0.10 were adjusted.[38] In accordance with Vannest and Ninci,[38] *Tau-U* effect sizes of $<0.20$ were considered small; 0.20 to $<0.60$, moderate; 0.60 to $<0.80$, large; and $\geq 0.80$, very large. Weighted *Tau-U* averages in exercise participants and stretching participants were calculated in each Block using an online Web-based calculator.[39]

## RESULTS

For picture-naming probe data, intrarater reliability was 99%, and inter-rater reliability was 98%. Probe data from each participant were graphed using SigmaPlot software (Systat Software Inc (SigmaPlot version 13.0), Chicago, Illinois; Figure 2, and see Supplemental Appendices in the online version at https://doi.org/10.1016/j.clinthera.2017.12.002). To investigate whether participation in aerobic exercise enhanced the effects of aphasia therapy, individual effect sizes in Blocks 1 and 2 of treatment were calculated using *Tau-U* (Table II). All participants responded to the aphasia treatment in both Block, with large to very large effect sizes in all participants except S2, who demonstrated a moderate effect in Block 2.

Weighted *Tau-U* mean values in Block 1, the control Block of therapy without the exercise or stretching adjuvant, indicated a very large effect in exercise participants (*Tau-U* = 0.83) and a large effect in stretching participants (*Tau-U* = 0.75). Thus, there were small group differences prior to the beginning of the exercise or stretching interventions. Weighted means in Block 2 of therapy also showed a very large effect in exercise participants (*Tau-U* = 0.88) and a large effect in stretching participants (*Tau-U* = 0.77). Both groups demonstrated an increase in *Tau-U* in Block 2, with exercise participants showing a larger change in weighted mean than that in stretching participants. However, due to the small sample size, it was not feasible to test whether this difference was statistically significant.

Basal serum BDNF concentrations are presented in Table III. The baseline BDNF levels in participants (ie, the 2 measures prior to the exercise or stretching interventions) showed a great deal of intraparticipant variation. Hence, in an attempt to minimize the intraparticipant variability, we calculated the mean values from samples 1 and 2 to obtain a baseline BDNF measure, samples 3 and 4 to obtain a BDNF measure in the first 6 weeks of aerobic exercise or stretching, and samples 5 and 6 to obtain a measure in the last 6 weeks of the exercise or stretching intervention. In all of the exercise participants (E1, E2, E3, E5), there was a drop in serum BDNF during the first 6 weeks of aerobic exercise, followed by varying degrees of recovery. This sequence of BDNF

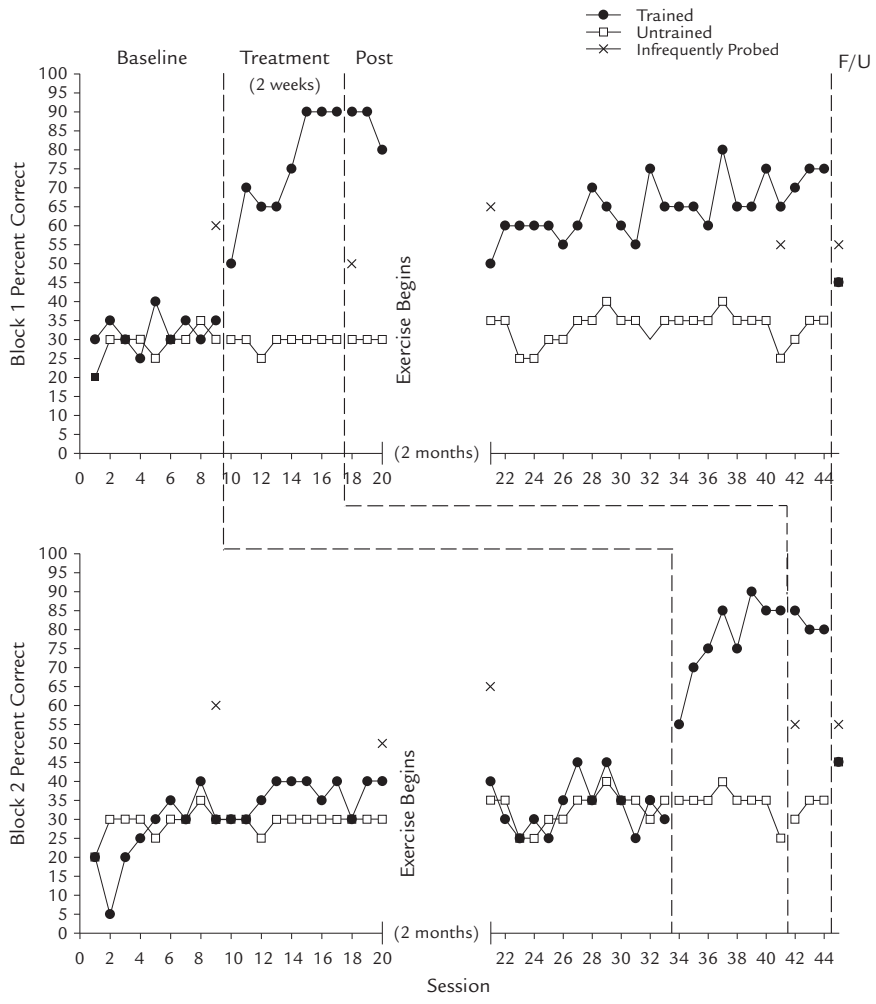


Figure 2. Picture-naming probe data for E3. Picture-naming probes are presented across baseline, treatment, and post-treatment for Blocks 1 and 2. Infrequently probed pictures were untrained. F/U = follow-up.

levels was not demonstrated in the stretching participant (Figure 3).

## DISCUSSION

The purpose of the present study was to determine whether participation in aerobic exercise enhances the effects of aphasia therapy. Using a single-patient, multiple-baseline design, we found that 3 of 5 participants demonstrated larger effect sizes in the second treatment Block when aphasia therapy was paired with aerobic exercise, whereas 1 of 2 participants demonstrated a larger effect size in the second treatment Block when aphasia therapy was paired with stretching. Due to the small sample size, it was not feasible to test whether effect sizes were significantly different within and across individuals who were in the exercise and stretching groups. However, group-level comparisons of the first and second treatment Blocks revealed a greater overall increase in effect size with aerobic exercise, as shown by differences in *Tau-U* weighted means across periods. In summary, our hypothesis that exercise would enhance aphasia treatment outcomes is partially supported by our results. However, due to the small sample size in the present study and to the control group of only 2 participants, these findings should be interpreted with caution.

An interesting finding was that all aerobic exercise participants demonstrated decreased BDNF concentrations during the first 6 weeks of exercise, followed by levels that then rose toward or reached

Table II. Estimates of cued picture-naming treatment effect size* using *Tau-U* in Block 1 and 2.

| | Block 1 | | | | Block 2 | | | |
|---|---|---|---|---|---|---|---|---|
| Participant† | Trained *Tau-U* | *P* | Effect | 85% CI | Trained *Tau-U* | *P* | Effect | 85% CI |
| E1 | 0.83 | <0.001 | Very large | 0.48–1.00 | 0.75 | 0.005 | Large | 0.37–1.00 |
| E2 | 0.66 | 0.007 | Large | 0.31–1.00 | 0.78 | 0.003 | Large | 0.40–1.00 |
| E3 | 0.95 | <0.001 | Very large | 0.57–1.00 | 1 | <0.001 | Very Large | 0.65–1.00 |
| E4 | 0.79 | 0.001 | Large | 0.41–1.00 | 0.94 | <0.001 | Very Large | 0.56–1.00 |
| E5 | 0.95 | <0.001 | Very large | 0.57–1.00 | .92 | <0.001 | Very Large | 0.54–1.00 |
| S1 | 0.71 | 0.003 | Large | 0.37–1.00 | 1 | <0.001 | Very Large | 0.62–1.00 |
| S2 | 0.79 | 0.003 | Large | 0.41–1.00 | .55 | 0.040 | Moderate | 0.16–.93 |
| E1-E5 weighted mean | 0.83 | <0.001 | Very large | 0.67–1.00 | 0.88 | <0.001 | Very Large | 0.71–1.00 |
| S1-S2 weighted mean | 0.75 | <0.001 | Large | 0.49–1.00 | 0.77 | <0.001 | Large | 0.50–1.00 |

*Effect-size interpretation was based on Vannest and Ninci.[38] Scale: <0.2 = small; 0.2 to <0.6 = moderate; 0.6 to <0.8 = large; ≥0.8 = very large.
†Participants E1 to E5 exercised on a bicycle ergometer; participants S1 and S2 stretched.

baseline during the last 6 weeks of exercise, but that the stretching participant did not show the same effect. One explanation for this finding is that the initiation of exercise may have induced a stress response in our poststroke population, characterized by a decreased BDNF level,[40] which was followed by recovery as the participant became more conditioned from regular aerobic activity. The pattern of BDNF concentrations raises an important question about whether the duration of our exercise intervention was long enough to obtain optimal effects. Erickson et al[41] found that after 1 year of exercising by walking at a pace sufficient to reach a target heart rate, many healthy community-dwelling older adults demonstrated increases in serum BDNF that correlated with increased hippocampal volumes after exercise. Thus, it is possible that our 3-month exercise intervention was not long enough, and that with additional exercise, serum BDNF would have risen to levels greater than baseline and would have produced greater behavioral gains. Future research should address the optimal length of exercise intervention prior to behavioral treatment in order to capitalize on maximal increases in BDNF.

Table III. Basal serum brain-derived neurotropic factor concentrations at baseline and during the first and last 6 weeks of aerobic exercise (E1, E2, E3, E5) or stretching (S2). Data are given as pg/mL.

| | Baseline | | | First 6 Weeks | | | Last 6 Weeks | | |
|---|---|---|---|---|---|---|---|---|---|
| Participant | Sample 1 | Sample 2 | Mean | Sample 3 | Sample 4 | Mean | Sample 5 | Sample 6 | Mean |
| E1* | 28654.66 | 23424.56 | 26139.61 | 23201.40 | 24425.40 | 23813.40 | 25852.40 | 27465.60 | 26659.00 |
| E2* | 21701.99 | 30441.81 | 26071.90 | 25677.69 | 22332.17 | 24004.93 | 28262.07 | 25549.13 | 26905.60 |
| E3* | 13886.19 | 9647.86 | 11767.03 | 11475.28 | 5506.41 | 8490.85 | 12302.75 | 8866.44 | 10584.60 |
| E5† | 34372.50 | 26106.0 | 30239.25 | 20695.50 | 11122.50 | 15909.00 | 13678.5 | 23202.00 | 18440.25 |
| S2† | 18126.00 | 21489.00 | 19807.50 | 23239.50 | 23388.00 | 23313.75 | 17323.50 | 22087.50 | 19705.50 |

*Processed using Human Free BDNF Quantikine ELISA Kit (R&D Systems, Minneapolis, Minnesota).
†Processed using Mature BDNF Rapid ELISA Kit (Biosensis, Thebarton, SA, Australia).

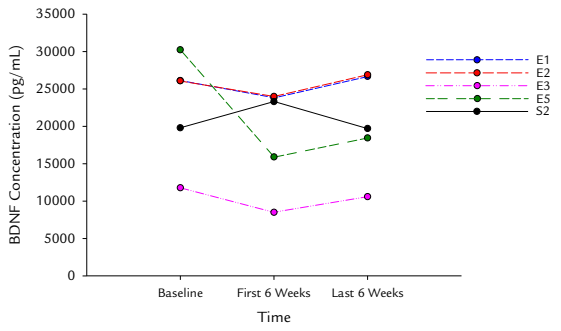


Figure 3. Serum brain-derived neurotropic factor (BDNF) concentrations, by participant. E1, E2, E3, and E5 were exercise participants. S2 was a stretching participant. Baseline is the mean of 2 blood draws that occurred before beginning exercise or stretching. First 6 weeks and last 6 weeks were each means of 2 blood draws that occurred during the beginning and end of the exercise/stretching intervention, respectively.

This study implemented a complex treatment design with factors related to the behavioral intervention (assessment and therapy) and the exercise intervention (aerobic exercise vs stretching). It is important to consider how the methodologic decisions about both interventions affected our outcomes.

## Considerations Related to Exercise Intervention

This study sought to capitalize on the beneficial effects of aerobic exercise on language[42] and cognitive function in previous studies involving older adults and individuals poststroke.[3,4,17,43] Interpretation of the results requires the consideration of crucial factors that include mechanisms of effect, timing, intensity, and individual factors.

### *Mechanisms of Effect*

The ability to optimize exercise as an aphasia therapy adjuvant relies on an understanding of the mechanistic effects of both acute (immediate) and long-term exercise. We collected blood samples to explore potential increases in basal serum BDNF levels related to long-term exercise. We found a decrease in BDNF in the first 6 weeks after the beginning of exercise, with an increase toward baseline during the next 6 weeks, a pattern not shared by our stretching participant. A systematic literature review[28] reported that although no findings from studies have shown long-lasting effects of exercise on increases in BDNF, there was evidence that exercise or training temporarily elevates basal BDNF, which returns to baseline 15 to 60 minutes after exercise termination.

In contrast to BDNF values obtained in animal studies, measuring human serum BDNF poses additional challenges due the influence of other factors, such as whether the sampling occurred after fasting and time of day of blood collection.[44] In the present investigation, participants did not fast prior to blood collection for BDNF, which may have introduced variability. Fasting blood draws in future research would remove this variability for more stable measurements. Moreover, sampling at the same time of day, or same time relative to sleep/wake cycles in each participant, may further decrease variability.[44]

Most mechanistic studies have focused on serum BDNF; however, other physiologic mechanisms detectable in blood also have been considered. For example, the novel word–learning studies discussed previously have shown that word learning can be enhanced by increases in BDNF and dopamine. Winter et al[24] found that serum BDNF and plasma dopamine levels were correlated with word-recall performance immediately after high-intensity exercise and 1 week later, respectively. Similarly, the administration of a dopamine precursor enhances word learning in healthy younger adults, with specific effects on lexical–semantics processing[45] and long-term retention of words.[45,46] Thus, in order to understand the mechanisms that may enhance treatment outcomes, future studies should consider exploring dopamine and other neurotransmitters, as well. Furthermore, we suspect that the pattern of BDNF fluctuations in the present study emerged due to a stress response in our participants who began aerobic exercise. Future studies should also consider collecting data on cortisol and other stress hormones to better understand the factors that modulate BDNF fluctuations and learning outcomes in poststroke individuals.

### *Timing*

As briefly mentioned earlier, the timing of behavioral interventions in relation to exercise warrants further research. It is plausible that, during the

initiation of an exercise regimen in relatively sedentary poststroke individuals, a stress response could occur, causing BDNF levels to dip below baseline. However, the present data suggest that with acclimatization to the exercise protocol, BDNF levels begin to rise. At this point, it is unclear whether continued exercise would have produced BDNF concentrations greater than baseline, but the present data show a consistent trend that BDNF levels were recovering toward baseline during weeks 7 to 12 of exercise.

Another question that arises from this study is the timing of exercise in relation to aphasia therapy (in Block 2). At the time this study was conceptualized, data on the rise and fall of BDNF levels with acute exercise were not available. Therefore, we decided to alternate between delivering aphasia therapy immediately after aerobic exercise and delivering aphasia therapy before exercise or on days that no exercise occurred, as a compromise between potential positive effects immediately after exercise and fatigue. Even now, the optimal timing of exercise remains an open question. For example, Salis[47] demonstrated that vigorous exercise before or after study improved performance on a vocabulary task in healthy young adults. Schmidt-Kassow et al[26] found that in young female adults, the acquisition of foreign vocabulary was enhanced when participants engaged in moderate exercise during learning as opposed to before learning. Thus, comparative studies are required to determine whether exercise before, during, or after intervention will yield the best outcomes in aphasia.

### *Intensity*

Although aerobic exercise has been shown to improve cognition and motor function poststroke,[2–4,7] it is possible that the exercise intensity in our participants was not optimal for achieving similar effects on language. A recent systematic review of data from studies in humans and animals investigated the relationship between poststroke aerobic exercise and brain-repair processes.[27] Although no studies in humans met the inclusion criteria, the findings from animal studies suggested that moderate-intensity exercise, which was 30% to 50% of the running speed capacity (eg, 10–12 m/min), was most effective in neurorehabilitative processes such as decreasing inflammation, promoting neurogenesis, and decreasing lesion size. The importance of exercise intensity has also been demonstrated in word-learning studies involving healthy young adults. For example, Winter et al[24] found that high-impact running (compared with low-impact running and rest) resulted in 20% faster word acquisition in younger male adults. Schmidt-Kassow et al[48] compared BDNF in low- versus high-intensity exercise, finding that BDNF increased only with high-intensity exercise. However, intensity-dependent BDNF increases have also been reported in studies in which increases were not associated with cognitive improvement.[36] Nonetheless, these findings from studies suggest that intensity may be a crucial factor in exercise intervention, and that higher intensity may be necessary for humans to achieve optimal results. However, with higher intensity comes greater fatigue, particularly in individuals with chronic stroke who may be deconditioned. In our study, participants exercised at 50% to 70% of their heart rate reserve. More research is required to identify optimal intensity, taking into consideration the effects of tolerance and fatigue.

### *Individual Factors*

Research into individual factors that influence response to exercise interventions has been limited, but there is some evidence that genetics and baseline cognitive ability may play an important role. For example, it has been suggested that individuals with *BDNF* polymorphisms have a decreased exercise-induced BDNF response, which may in turn affect BDNF-mediated behavioral outcomes.[28] We did no testing for *BDNF* polymorphisms. However, recent findings suggest that the *BDNF* Val66Met polymorphism may not negatively impact language recovery soon after a stroke.[49]

With regard to individual factors, studies have also shown that those who perform lowest at baseline benefit the most from exercise. For example, Sibley and Beilock[50] demonstrated that individuals with the lowest baseline working memory ability showed the greatest improvements on a working memory task following a single bout of exercise. Similarly, Schmidt-Kassow et al[26] found that acute exercise yielded the greatest improvements in foreign vocabulary learning in individuals with the lowest verbal memory capacity. In our study, participants who exhibited the lowest effect sizes in the first treatment Block had the greatest increase in effect sizes during the second treatment Block when aphasia therapy was paired with aerobic exercise; however, the effect size pattern across periods also occurred in a stretching participant, so it is unclear whether the effect size pattern across periods is related to exercise or greater room for improvement (eg, the

absence of a ceiling effect in these participants). Nonetheless, additional research into individual factors is important for identifying patients who may benefit most from an exercise-based intervention.

## Considerations Related to Behavioral Intervention

Additional behavioral considerations include the impact of an order effect and probing schedule on the effects of intervention. Frequent probing of picture stimuli during baseline, before each treatment session, and after treatment in each Block of therapy exposed participants to trained and untrained stimuli on a regular basis, which may have affected performance. PWAs often produce incorrect responses on probe items before training, which may result in items trained in the second Block of therapy becoming more resistant to treatment-induced changes because errors were reinforced before treatment was initiated.

All participants received anomia therapy alone during the first treatment Block and aphasia therapy with the addition of aerobic exercise or stretching during the second treatment Block. Although the use of a crossover approach would help to mitigate an order effect, it poses a design challenge due to the potential physiologic changes from exercise. Participants engaging in aerobic exercise during the first Block of therapy would have required a sufficient washout Block to prevent any exercise-related improvements in the second therapy Block. Moreover, there are ethical concerns with asking participants to discontinue exercise due to the beneficial effects of exercise on overall health.

It is also possible that our exercise intervention had positive effects on cognitive function that were not adequately captured by the naming probes alone. There is evidence that some cognitive functions are more likely to improve with exercise,[51] and that only certain cognitive functions are related to aphasia treatment outcomes.[16] Future studies should include pre- and post-treatment assessments of a broad range of cognitive functions to enhance our understanding of the relationship between aerobic exercise, cognitive functions, and treatment outcomes in aphasia rehabilitation.

## Future Directions

We have only begun to understand the potential for exercise-based interventions in aphasia. More research is required to determine how the acute and long-term effects of exercise may be harnessed to improve treatment outcomes. It has been suggested that understanding the acute effects of exercise is important in the development of exercise-based interventions in neurologic disease.[52] Indeed, a greater understanding of the benefit of single exercise sessions is important for understanding the accumulating benefit of those single sessions over time (ie, long-term exercise effects). Future studies may use acute exercise paradigms as an efficient way of identifying individual and task-based variables associated with successful exercise-based interventions and to investigate transient neurophysiologic effects of exercise that may underlie exercise-induced improvements in cognitive and language tasks.

One paradigm that may be used for optimizing acute exercise effects is novel word learning. Novel word–learning paradigms have been used successfully to investigate verbal learning ability in aphasia[53–55] and to investigate the potential of neuromodulatory approaches to improve word-retrieval interventions in aphasia.[56] Basso et al[57] showed that methods of enhancing new word learning in older adults are efficacious in word relearning in individuals with aphasia. The emerging body of literature on novel word learning provides support for the use of acute exercise as an adjuvant to aphasia treatment.[24,26,47,48,58] This evidence on improved word learning in healthy young adults has recently been extended to older adults whose physical activity level and brain structure and function may be similar to those of the majority of PWAs.[59] Moreover, Dignam et al[60] recently demonstrated that novel word–learning ability in PWAs was significantly positively correlated with the ability to name treated items immediately after treatment. These findings suggests that cognitive processes involved in novel word learning may contribute to acquisition (or relearning) of words in aphasia.[61] Thus, the converging evidence that exercise enhances novel word learning and that novel word–learning ability is positively correlated with aphasia treatment outcomes provides support for utilizing novel word learning as a paradigm to investigate how acute exercise may be used as an adjuvant to aphasia treatment. CPNT is a well-controlled naming treatment paradigm that allows for structured comparison between different conditions; however, it does not provide information about changes in functional communication abilities. Future studies should also investigate whether exercise-enhanced changes on naming skill acquisition generalize to functional communication abilities, or whether exercise facilitates enhanced performance when used in combination with functional

communication treatment approaches, such as the Life Participation Approach to Aphasia.[62]

Although the present study is the first to demonstrate the effects of aerobic exercise on poststroke aphasia therapy outcomes, due to the small sample size we recommend cautious interpretation of the results. Future research is needed to replicate the present findings in a larger sample and to advance this line of inquiry. In addition, future research should include an evaluator who is blinded to treatment conditions or groups to limit potential bias.

Aerobic exercise and stretching were tolerated in all of the participants in the present investigation. There were no instances in which participants were unable to complete study activities due to acute fatigue. Some participants provided informal feedback that they felt good about having begun an exercise program. A mixed-model approach utilizing both structured surveys (ie, quantitative data collection) and open-ended interviews (ie, qualitative data collection) about the experience of poststroke individuals participating in exercise would provide more detailed information that may help to inform future work.

## CONCLUSIONS

To our knowledge, this is the first published study incorporating exercise as an adjuvant to aphasia treatment. The results of our study suggest that more research is needed to understand the potential of exercise as a means of enhancing treatment outcomes. Converging evidence from the literature on the long-term and acute effects of exercise on learning and memory compels us to continue this investigation, with consideration of the importance of understanding the mechanisms of effect and identifying the factors that mediate response to exercise interventions, including optimal dose of exercise and timing of language intervention with exercise.

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## AUTHORS' CONTRIBUTIONS

Stacy Harnish contributed to the literature search, study design, figure creation, data collection, data interpretation, and writing. Amy Rodriguez contributed to the literature search, figure creation, data interpretation, and writing. Deena Schwen Blackett contributed to figure creation, data interpretation, and writing. Christopher Gregory contributed to study design, data interpretation, and writing. Lauren Seeds contributed to data collection, data interpretation, and writing. Jeffrey Boatright contributed to data analysis, data interpretation, and writing. Bruce Crosson contributed to the literature search, study design, figure creation, data interpretation, and writing.

## CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

## SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.clinthera.2017.12.002.

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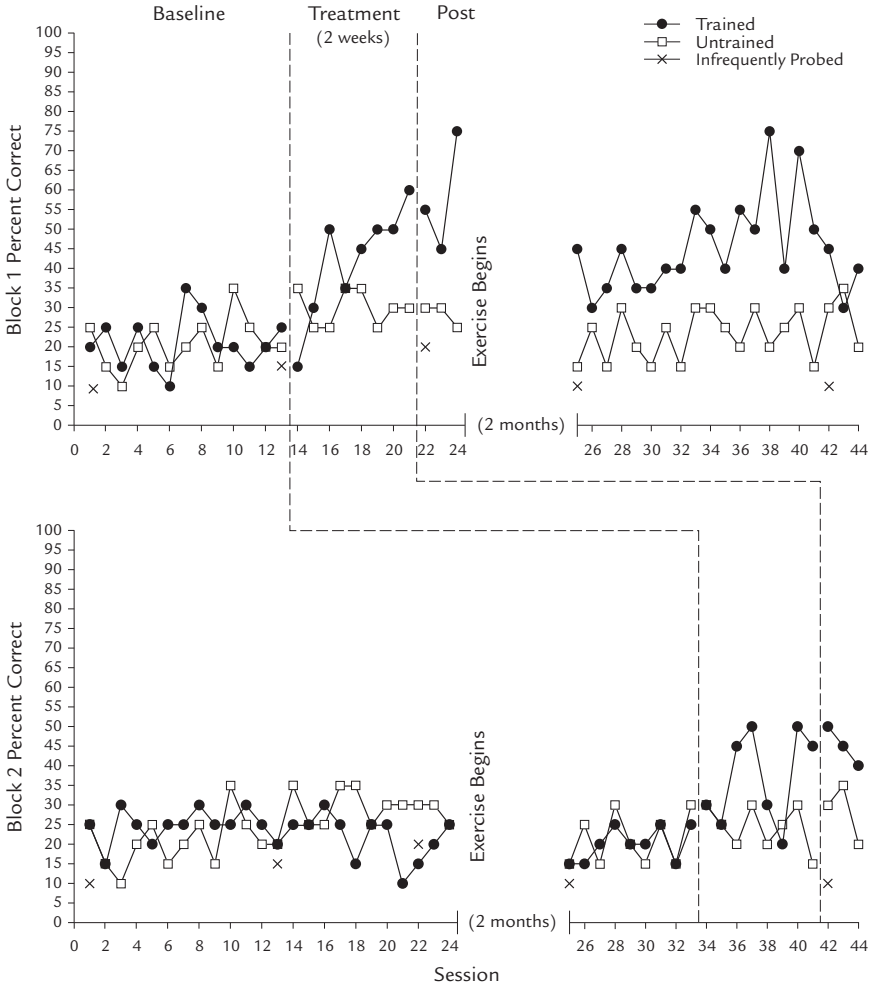
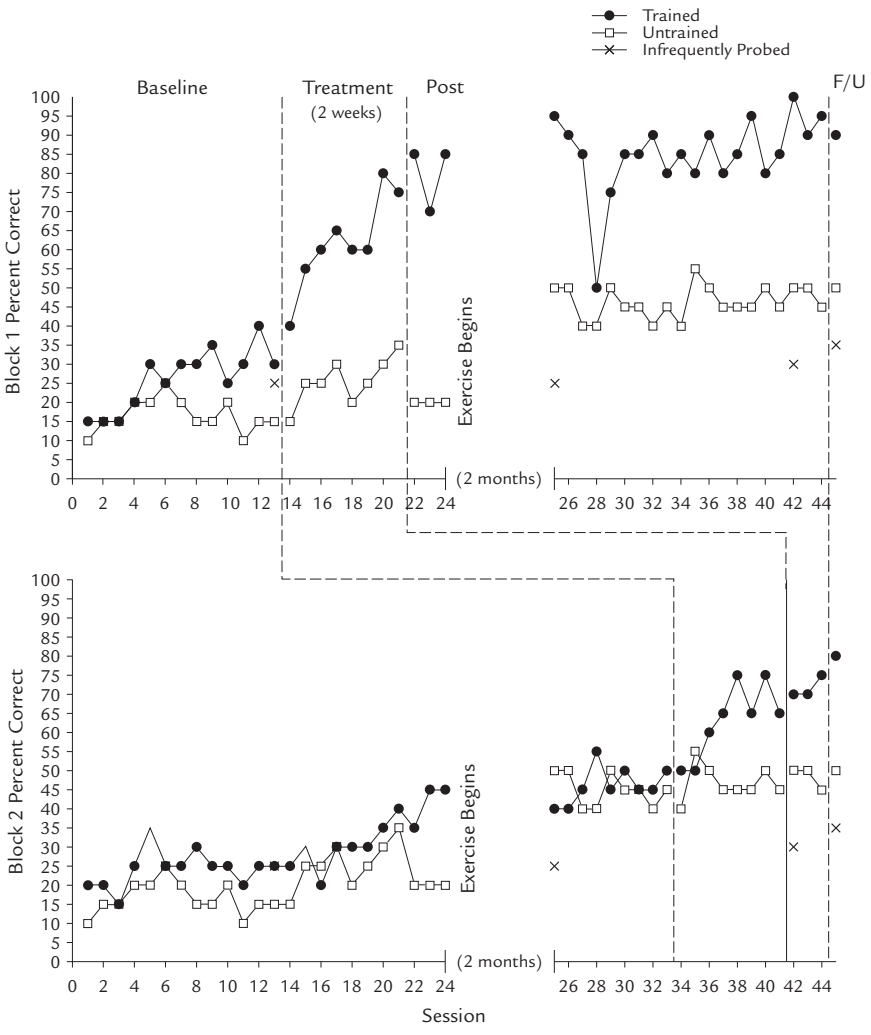
## SUPPLEMENTARY MATERIAL

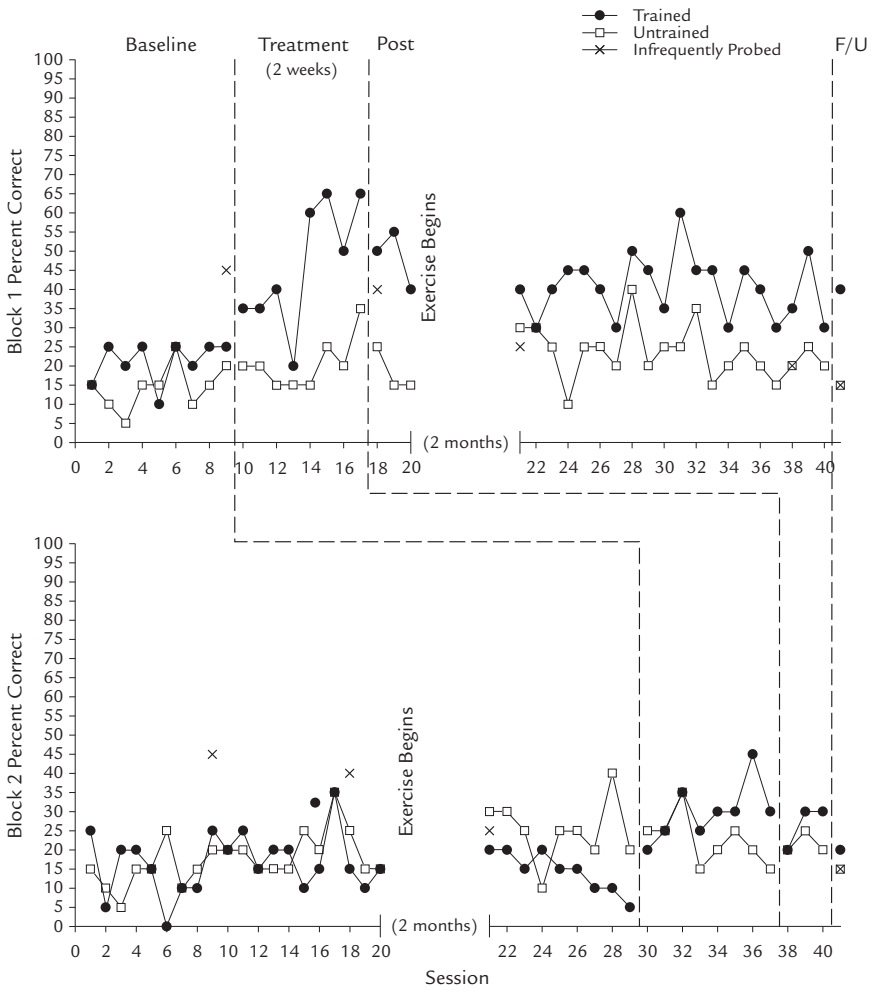
### Appendix 1–6



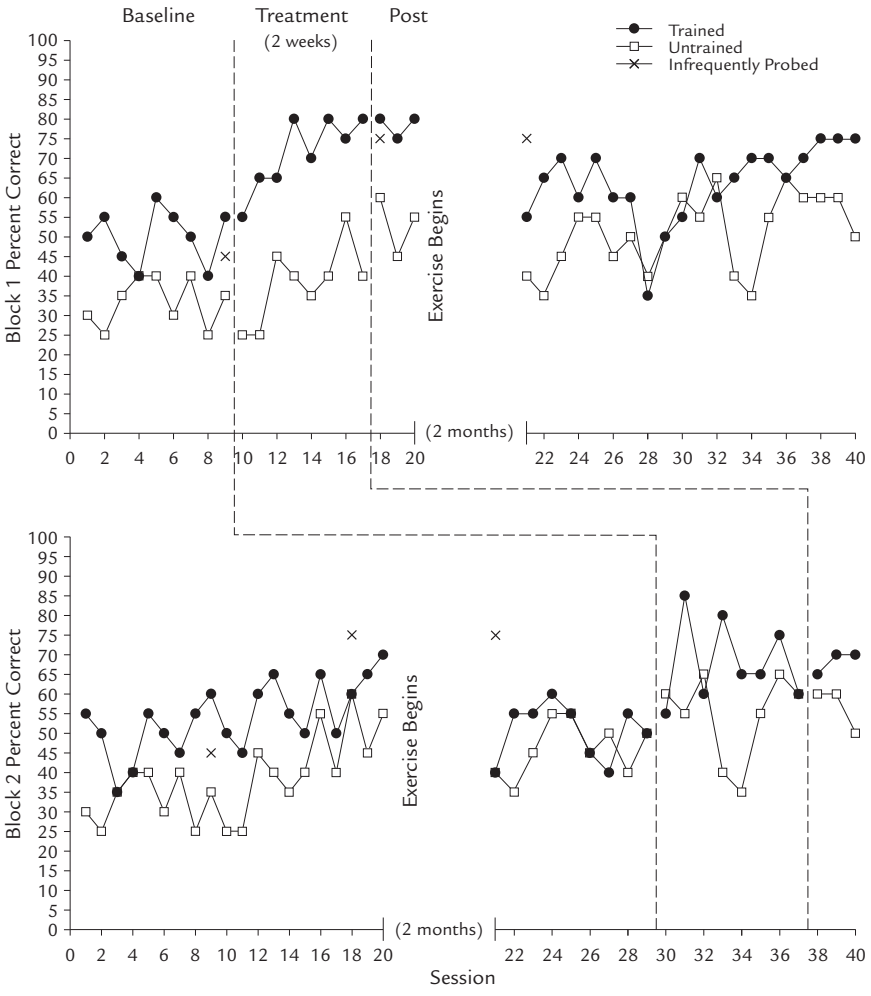

Appendix 1. Picture-Naming Probe Data for E1. *Picture-naming probes are presented across baseline, treatment, and post-treatment for Block 1 and Block 2. Infrequently-probed pictures were untrained. An extra infrequently-probed data point was included in the baseline phase for this participant and is included in the graph. The participant did not return for follow-up.*



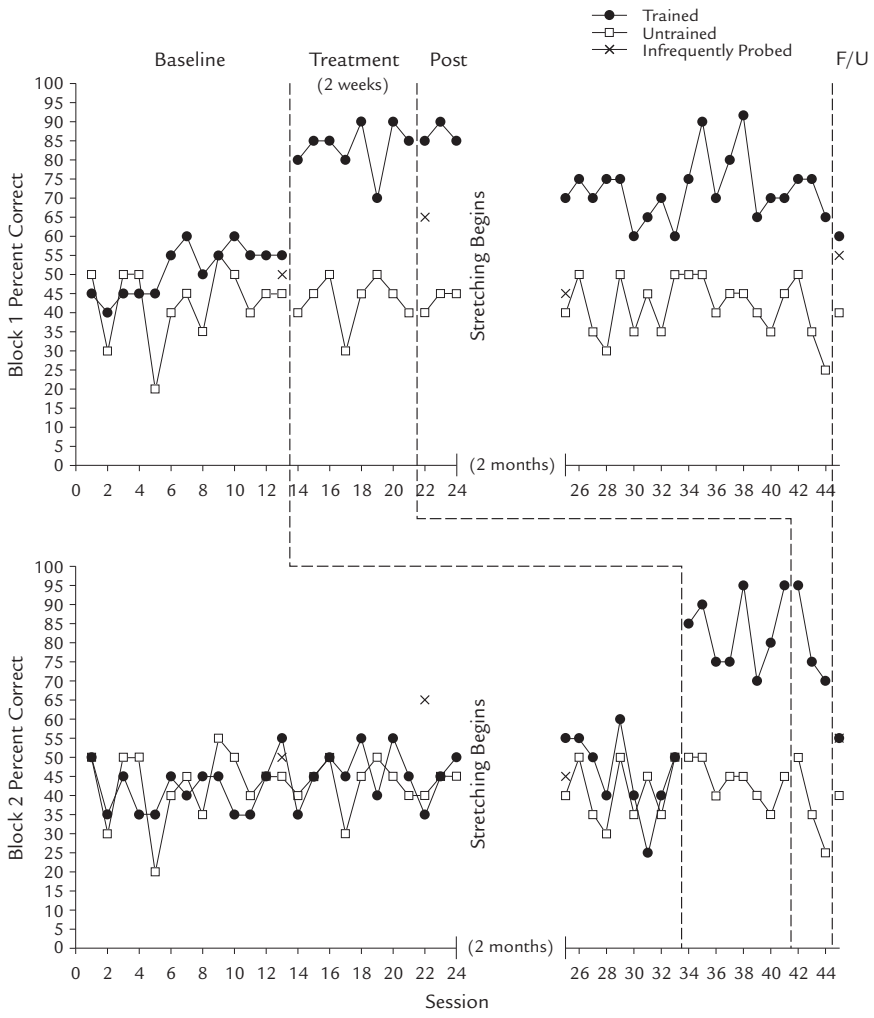

Appendix 2. Picture-Naming Probe Data for E2. *Picture-naming probes are presented across baseline, treatment, and post-treatment for Block 1 and Block 2. Infrequently-probed pictures were untrained. There is a missing data point for infrequently probed Block 1, post-treatment because in error, the data were not collected.*



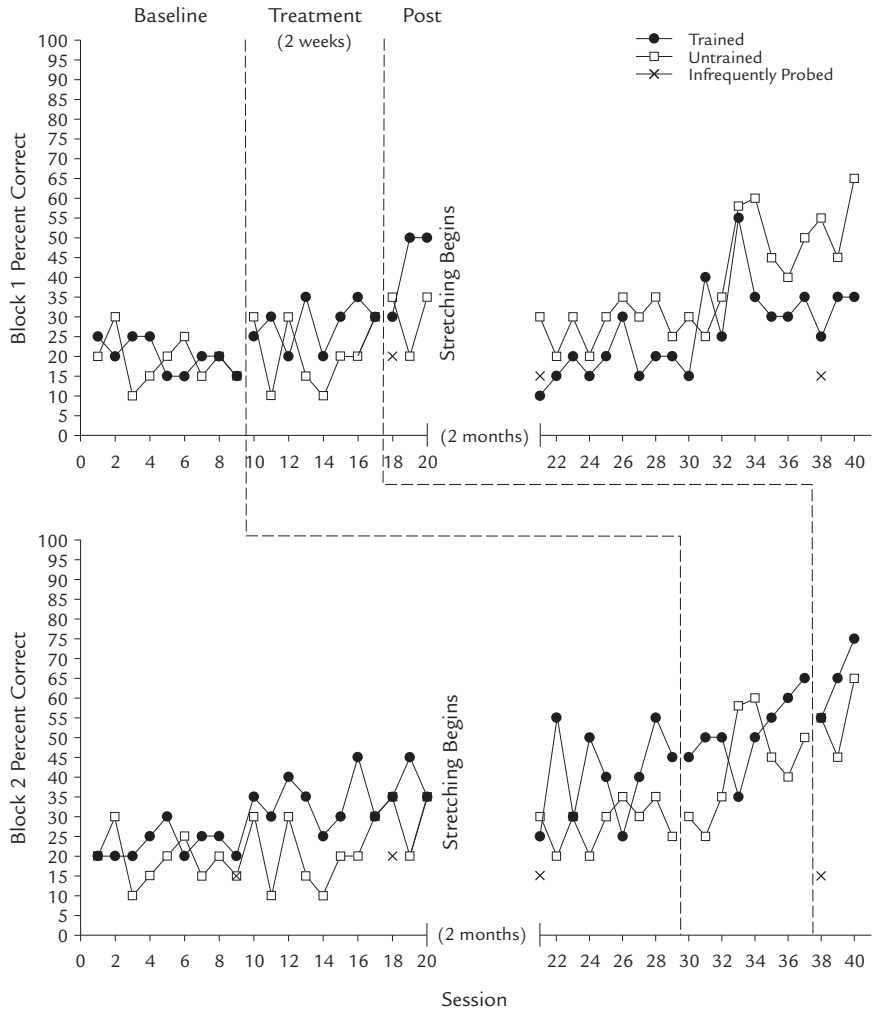

Appendix 3. Picture-Naming Probe Data for E4. *Picture-naming probes are presented across baseline, treatment, and post-treatment for Block 1 and Block 2. Infrequently-probed pictures were untrained.*




Appendix 4. Picture-Naming Probe Data for E5. *Picture-naming probes are presented across baseline, treatment, and post-treatment for Block 1 and Block 2. Infrequently-probed pictures were untrained. There is a missing data point for infrequently probed at Block 2 post-treatment because in error, the data were not collected. The participant did not return for follow-up.*




Appendix 5. Picture-Naming Probe Data for S1. *Picture-naming probes are presented across baseline, treatment, and post-treatment for Block 1 and Block 2. Infrequently-probed pictures were untrained. There is a missing data point for infrequently probed at Block 2 post-treatment because in error, the data were not collected.*




Appendix 6. Picture-Naming Probe Data for S2. *Picture-naming probes are presented across baseline, treatment, and post-treatment for Block 1 and Block 2. Infrequently-probed pictures were untrained. The participant did not return for follow-up data collection.*