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Speech Entrainment for Aphasia Recovery (SpARc) phase II trial design

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ABSTRACT

Background: and purpose: Speech entrainment therapy (SET) is a computerized therapeutic approach that involves mimicking an audiovisual speech model to improve speech production. In a pilot study using SET for treatment of post-stroke non-fluent aphasia, significant gains were achieved in verbs per minute (VPM) during discourse using untrained items 1 and 6 weeks after treatment, suggesting that SET may yield meaningful improvements in fluent spontaneous speech for individuals with non-fluent aphasia.

Methods: The Speech Entrainment for Aphasia Recovery (SpARc) trial is a prospective, randomized, assessor-blinded, multicenter phase II clinical trial studying persons with chronic post-stroke non-fluent aphasia. Participants will be randomized to 3 weeks, 4.5 weeks, or 6 weeks of SET delivered via telehealth or a no SET control condition for 6 weeks. 80 adults (ages 21–81) with history of left hemisphere ischemic or hemorrhagic stroke with residual chronic (>6 months post stroke) non-fluent aphasia diagnosed by the Western Aphasia Battery-Revised (WAB-R) will be randomized (1:1:1:1) over 4 years. The trial will be conducted at the clinical research facilities at three sites: the Medical University of South Carolina, the University of South Carolina, and the University of Utah.

Conclusions: This paper details the trial design of the SpARc trial, which aims to determine the dose of SET that will generate the highest effect size on speech fluency, VPM, sustained at 3 months post-treatment compared to a no SET control arm, for individuals with chronic post-stroke non-fluent aphasia to permit a future definitive trial to test the clinical utility of SET.

1. Introduction

Non-fluent aphasia is defined by significantly reduced speech production, ranging from total mutism to utterances composed of only 3–5 words [1,2]. Non-fluent aphasia is not only a very common type of aphasia, affecting approximately 40% of all chronic aphasia cases [3], but also one of the most debilitating types. Unfortunately, non-fluent aphasia is frequently associated with profound frustration and depression [4].

It is relatively uncommon for individuals with non-fluent aphasia to recover to a point where their speech could be considered fluent with the existing therapies, particularly in the chronic phases after the stroke [5,6].

In a preliminary study [7], we reported Speech Entrainment Therapy (SET) as a new form of speech therapy to enable individuals with non-fluent aphasia to produce fluent speech. This therapy uses an audiovisual computer system to guide (*entrain*) the speech of the person with aphasia, i.e., the person with aphasia verbally mimics the speech from the audiovisual program in real-time. In our original study, we observed that many participants with non-fluent aphasia overcame the barrier towards fluency and achieved improvements in fluent speech with SET, with normal prosody and without worsening errors [7]. Since then, we expanded our pilot data, and we observed that individuals with non-fluent aphasia treated with SET achieved greater than 20% improvement in verbs per minute (VPM) during spontaneous speech at 3

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Abbreviations

SET	speech entrainment therapy
VPM	verbs per minute
WAB-R	Western Aphasia Battery-Revised
MUSC	Medical University of South Carolina
UofSC	University of South Carolina
UoU	University of Utah
AQ	aphasia quotient
NIHSS	NIH Stroke Scale
SLP	Speech-Language Pathologist
ASRS	Apraxia of Speech Rating Scale
PRT	Philadelphia Repetition Test
PNT	Philadelphia Naming Test
PPTT	Pyramids and Palm Trees Test
WAIS	Wechsler Adult Intelligence Scale
SAQOL-39g	Stroke and Aphasia Quality of Life Scale
CETI	Communicative Effectiveness Index
SADQ-10	Community Stroke Aphasic Depression Questionnaire
CLAN	Computerized Language ANalysis
MCID	minimally clinically important difference
ITT	intent-to-treat
CIAT	Constrained-Induced Aphasia Therapy
TMS	transcranial magnetic stimulation
MIT	Melodic Intonation Therapy

months post-treatment. These results are encouraging because they represent sustained post-treatment gains in producing verbs during discourse, which is a valid ecological measure that is a better predictor of language abilities compared with producing nouns or object naming [8].

We believe that SET is unique and perhaps superior to other forms of therapy because it enables individuals with aphasia to practice relatively error-free fluent speech, while other existing forms of speech therapy unfortunately tend to produce frequent errors, which may percolate outside the therapy setting. More specifically, the basic premise behind most rehabilitation approaches, regardless of the targeted function or modality, is that repeated practice of a specific behavior within the therapy session leads to an increased likelihood that this behavior can be repeated outside the rehabilitation setting. This concept is related to the principle of Hebbian learning, which is based on the notion that synaptic strength and functional neuronal connections can be reinforced due to repeated stimulation [9] and new experiences lead to molecular and cellular events that alter synaptic efficacy, leading to reorganization of neuronal circuits [10].

This principle should be considered in the context of aphasia therapy since conventional therapies typically induce numerous speech errors [5,6]. In fact, treatment-induced errors can often exceed correct responses [11]. Based on the Hebbian learning principles of neuroplasticity, it is possible that repeated errors could lead to maladaptive changes and contribute to the persistence of post-therapy errors and non-fluent speech. In contrast with conventional speech therapies, SET enables individuals with aphasia to practice fluent speech with relatively fewer errors, which is otherwise unachievable. SET guides the reestablishment of speech fluency, thus overcoming the initial barrier between non-fluent to fluent speech. However, how much SET can be of benefit is unknown.

2. Methods and design

Speech Entrainment for Aphasia Recovery (SpARc) is an NIH funded multi-site, prospective, controlled, randomized, assessor-blinded phase II clinical trial with the goals to evaluate SET for non-fluent aphasia in comparison with no SET, and to determine the dose of SET (duration of treatment in weeks) with the highest effect size. It will take place at the Medical University of South Carolina (MUSC), University of South Carolina (UofSC), and University of Utah (UoU). Written, informed consent is obtained from each participant or their legally authorized representative using the IRB approved consent process. Eligible participants with non-fluent aphasia are randomized into one of four arms. There are three treatment arms (see Fig. 1): Arm A (3 weeks of SET), Arm B (4.5 weeks of SET), and Arm C (6 weeks of SET). The fourth arm, Arm D, is the control condition which receives assessments at the same intervals as Arm C, but does not receive SET or any formal treatment. Outcome measures will be assessed at 1 week, 3 months, and 6 months post SET or no SET.

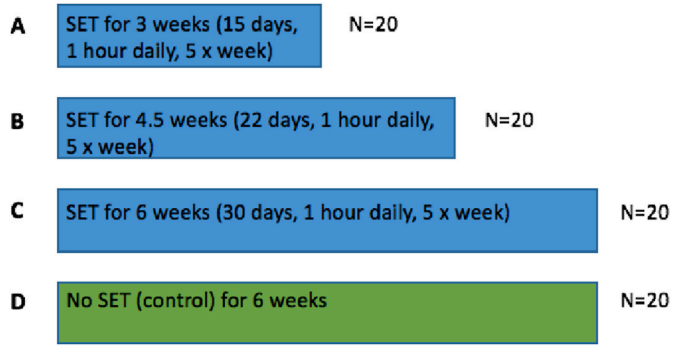

Fig. 1. SET dose for four Arms. Arms A, B, and C receive SET for 3, 4.5, and 6 weeks, respectively, while the control condition, Arm D, receives assessments at the same intervals as Arm C, but does not receive SET or any formal treatment.

2.1. Aims and hypothesis

The specific aim for SpARc is to determine the dose of SET with the highest effect size for individuals with non-fluent aphasia. We hypothesize that for individuals with chronic (>6 months) post-stroke non-fluent aphasia with relatively preserved speech comprehension (i.e., Broca's or transcortical motor aphasia, excluding global aphasia), SET will lead to sustained improvements in spontaneous speech production at 3 months post-treatment.

2.2. Study population

Participants include individuals with a history of ischemic or hemorrhagic left hemisphere stroke. The presence of non-fluent aphasia will be indicated by an aphasia quotient (AQ) < 93.8 on the Western Aphasia Battery-Revised (WAB-R), and an auditory Verbal comprehension score >4 and a fluency score <6. See Table 1, below, for inclusion and exclusion criteria.

2.3. Randomization

Eligible participants are randomized to one of four arms through a "real-time" randomization procedure implemented on the trial website for the Data Coordination Unit system at MUSC, WebDCU™. The procedure balances overall treatment distribution as well as the distribution of three important baseline covariates: clinical center, age (≤70, >70), and aphasia severity (mild/moderate, severe/very severe). The arm assignment will be based on the current status of the treatment arm

Table 1
Inclusion and exclusion criteria for SpARc.

Inclusion	Exclusion
Aphasia as a result of a left hemisphere ischemic or hemorrhagic stroke (WAB-R AQ <93.8)	History of chronic neurological or psychiatric diseases (with the exception of migraines, depression, or post-stroke epilepsy)
Presence of left hemisphere stroke in clinical imaging (CT/MRI) and NIHSS	Self-reported history of learning disability
English spoken as primary language	Severe dysarthria (determined via SLP clinical judgment from spontaneous speech tasks on the ASRS 3.0)
21–81 years old	Global aphasia
Pre-stroke modified Rankin Scale (mRS) = 2 or less	History of right-hemisphere strokes or brain stem/cerebellar strokes with persistent deficits (as evidenced by MRI/CT and NIHSS)
Post-stroke mRS = 4 or less	Uncorrectable hearing as determined by the SLP's clinical judgment
At least 6 months post-stroke	Uncorrectable vision as determined by the SLP's clinical judgment
Non-fluent aphasia: WAB-R comprehension score >4 and WAB-R fluency score <6	
Technological compatibility (to be determined by clinical judgment of SLP)	

distribution at each site, within each stratum (clinical characteristic), as well as the overall balance of treatment assignments.

2.4. Intervention

Participants randomized to Arm A, B, or C will receive SET for the specified dose (3, 4.5, or 6 weeks, respectively) for 1 h a day 5 days a week (typically Monday-Friday, but weekend days can replace work-week days). Treatment will be provided through telehealth in the form of an audiovisual computer program with a Speech-Language Pathologist (SLP) or research staff trained by an SLP (i.e., graduate student of speech-language pathology). Wearing a headset, the participant will be instructed to watch and listen to a video of a person speaking. The video's focal point is the actor's mouth, an image below the nose and including the chin. From a pool of 39 recorded scripts, the SET computer program (SEAS app) will randomize the presentation of each script. Following an initial script viewing, the participant will be instructed to speak with the video, mimicking what the actor is saying in real-time. The participant will receive three opportunities to speak along with the actor. SET will, therefore, guide (entrain) the speech of the person with non-fluent aphasia, improving overall fluent speech with normal prosody and without many errors [7].

2.5. Control condition

Participants randomized to Arm D, will not receive SET but will be contacted weekly via phone to assess adverse events and concomitant aphasia therapy. No treatment will be provided. Because this study includes individuals with chronic aphasia, and spontaneous language recovery is not typically observed at this stage, the expected change of language functioning during the no-treatment condition is expected to be very minimal, if any. The control condition will have the same schedule of follow-up visits as the treatment arm with the longest duration of SET (Arm C).

2.6. Baseline assessments

All individuals with aphasia are screened for inclusion in the study. Those screened and deemed ineligible for the study are entered onto a screening log which outlines the reason for non-inclusion. Details for recruitment and screening are outlined in the main trial protocol.

The assessment timeline is outlined in Table 2. Baseline assessments occur at least 6 months post-stroke. Assessments will occur over a 5 day period, depending on the testing needs of the participant. Participants are administered the WAB-R to determine presence of non-fluent aphasia and, therefore, eligibility. An MRI or head CT scan from the medical record is reviewed to confirm presence of left hemisphere stroke. A battery of cognitive-linguistic assessments is administered for the purpose of patient description, including presence of apraxia of speech via the Apraxia of Speech Rating Scale (ASRS) 3.0 [26,27], participant's ability to repeat via the Philadelphia Repetition Test (PRT), ability to name nouns via the Philadelphia Naming Test (PNT), semantic processing of nouns via the Pyramids and Palm Trees Test (PPTT) [28], and non-verbal abstract problem solving and inductive and spatial reasoning via the Weschler Adult Intelligence Scale (WAIS) III [29]. Participants are also assessed for quality of life and communicative effectiveness via the Stroke and Aphasia Quality of Life Scale (SAQOL-39g) [30] and the Communicative Effectiveness Index (CETI) [31]. We will also collect baseline characteristics including:

- Cardiovascular risk factors (Charlson Comorbidity Index [32])
- Pre-morbid functioning (Lexical Orthographic Familiarity Test [33])
- Post-stroke depression (Community Stroke Aphasic Depression Questionnaire [SADQ] −10 [34])
- Post-stroke fatigue (Epworth Sleepiness Scale [35] [modified for those with aphasia] and a non-verbal visual analogue of the fatigue severity scale developed in-house [36–38])
- Socio-demographic information including age, sex, race/ethnicity, handedness, pre-stroke household income, education level, insurance status, and marital status

Discourse samples are taken at baseline to assess VPM, the primary outcome measure for this trial (further discussed in Outcomes section). We will implement the use of both procedural storytelling items and narrative items from the AphasiaBank [39] protocol and analyze VPM using the discourse transcription and analysis tools: transcribed in Codes for the Human Analysis of Transcripts (CHAT) format and coded for analysis with Computerized Language ANalysis (CLAN) programs available through AphasiaBank.

Table 2
Study schedule.

Assessment/Case Report Form	Baseline	1 week post-treatment	3 months post-treatment	6 months post-treatment
Informed consent, collection of individual demographic and baseline characteristics, randomization	X			
VPM (discourse speech samples)	X	X	X	X
WAB-R	X	X	X	X
SAQOL-39g	X	X	X	X
CETI	X	X	X	
ASRS	X	X	X	
PPTT	X			
WAIS	X			
PRT	X	X	X	
PNT	X	X	X	
Adverse Event	O	O	O	O

X = required; O = optional/repeatable.

2.7. Outcomes

The primary outcome measure for this trial is VPM. It was chosen as the primary outcome because the use of verbs during spontaneous speech provides a reliable measure of language abilities and effectiveness of communication [8]. Spontaneous speech is an important "real-life" aspect of language. It has a direct effect on conversation and social aspects of language, and directly informs on practical and meaningful elements of communication.

In a preliminary study by our group [7], participants who underwent SET produced more words during discourse using untrained items 1 week (mean improvement = 17% [SD 1.7%], p = 0.009) and 6 weeks after treatment (mean improvement = 10% [SD 1.6%], p = 0.02).

We performed a subsequent and independent assessment of SET to directly mirror the approach proposed in this trial, with a similar endpoint, but uncontrolled and with a single group. Using assessors who were blinded to time of speech assessment, we examined 15 individuals with chronic non-fluent aphasia who were tested before and after 3 weeks of daily SET sessions. Similar to our preliminary study mentioned above, all participants were able to produce more fluent speech during SET therapy sessions. More importantly, there were considerable gains in spontaneous speech production that were sustained 3 months after SET. SET was also associated with an increase in ratings of information content. We observed an increase from a mean (SD) of 5.0 (3.9) VPM prior to therapy to 6.1 (4.8) VPM at 3 months after the conclusion of SET. The average relative improvement was 22% (average post-pre difference of 1.11 [1.98]), with a standardized effect size (mean difference/SD of difference) of 0.56 (p = 0.047).

In the SpARc trial, the primary outcome, VPM, is assessed at baseline, 1 week, 3 months, and 6 months post SET or no SET. As mentioned previously, VPM will be analyzed through discourse speech samples using the AphasiaBank protocol. Speech samples for VPM scoring will be assessed through procedural storytelling and narrative – with four items in each category. The participant will be recorded while describing each procedure. A 2-min time limit will be imposed for each item. The four topics will be randomized with only one topic being presented each time VPM is being assessed without topic repetition. Randomization of topics will be performed in WebDCU™.

By combining procedural storytelling and narratives ranging from different topics, a broad sample of discourse abilities will be obtained. They will be scored using automated coding analysis (CLAN) systems available through AphasiaBank. VPM is included in AphasiaBank and our data will be compared against the data from >440 aphasic participants already included in AphasiaBank. This feature is especially important for determining variance across participants.

The secondary outcome for this trial is the SAQOL-39g. Exploratory outcomes include the CETI and ASRS 3.0.

2.8. Blinding

The research staff and participants are not blinded to Arm, but the speech-language pathologist (SLP) scorers of the behavioral outcome measures are blinded. The SLP scorers are centrally located at UofSC and do not have contact with the on-site SLP, trained research staff, or the participants. Scoring is performed on video-taped behavioral assessments. There are no time stamps on the assessments and the assessors do not know if the sample was obtained before SET (or no SET), or at which time point after SET (or no SET) they were obtained. By having the same number of follow-up visits, the scorers are not able to discern the arm to which the participant was randomized. This setup was used successfully in a recently completed randomized controlled trial [40].

A second centralized SLP will score 20% of all assessments, including baseline testing and outcome measures, to establish inter-rater reliability. In addition, the primary coding SLP will rescore at least 20% of all assessments to establish intra-rater reliability.

2.9. Testing and treatment fidelity

Across all project sites, training of SLPs and research staff involved in testing and treatment is standardized. This involves the use of a detailed manual of treatment and assessment procedures. Fidelity of testing and treatment will be reviewed throughout the duration of the trial. For each subject, two assessments (a different set of assessments for each subject) will be recorded and submitted to be reviewed by the SpARc SLP Program Manager according to the standardized fidelity review protocol. Similarly, for each subject, two SET sessions will be recorded and reviewed by the SLP Program Manager against the trial's Treatment Fidelity Observation Form. Expert feedback will be provided as needed. Testing and treatment fidelity measures protect against potential threats such as variability in clinician qualifications, drift (gradual change in study procedures over time), contamination (systematic or variable influence of outside factors not controlled for in the study design), and clinician turnover.

2.10. Statistical analysis

2.10.1. Sample size considerations

This study will randomize 80 participants over 4 years. This study is not powered to detect statistically significant differences between the chosen SET dose and the control arm. This will be the focus of a later and dedicated comparison study once the best dose has been defined. The following pre-specified rule will be used to select best SET duration:

1. Highest effect size: highest standardized mean difference in VPM from baseline to 3 months post-treatment; and
2. Adequate tolerability: arm average participation in at least 80% of the treatment sessions.

The duration associated with the highest arm average VPM at 3 months post-treatment, and adequate tolerability, will be selected to move forward to a definitive trial.

A 20% improvement is considered a minimally clinically important difference (MCID) in this study. The MCID for this study therefore corresponds to an increase of 1 VPM based on our pilot data (20% of 5 VPM). For each treatment arm versus control the standardized mean difference (effect size) will be estimated. The criteria needed to accept any duration is that the effect size is at least 0.36 (a "small" to "medium" effect size). This criteria was chosen to take into account the potentially large standard deviation, given that this is an early phase clinical trial with a small sample size. Given the MCID = 1 and the common SD of change in VPM estimate from pilot data of 2, we expect the effect size to be 1/2 = 0.5. However, with n = 20 per arm, observed SD may be as large as 2.74 (i.e. a one-sided upper 95% confidence interval for SD = 2 is 2.74), thus the observed effect size may be only 1/2.74 = 0.36.

2.10.2. Primary analysis

We hypothesize that, compared to participants who are randomized to the control arm, participants who receive SET for 3, 4.5, or 6 weeks will have improved VPM at 3 months post-treatment, and that there is an optimal duration of SET. SpARc was not designed to formally test SET versus control, rather this study represents the first step in a series of studies which will ultimately test this hypothesis. For this study, no formal hypothesis tests are planned. The primary analyses will be descriptive statistics of VPM at 3 months post-treatment and will estimate the effect size of SET versus control, adjusting for baseline.

The pre-specified rule to select the best SET duration will be based on 1) the highest standardized mean difference (effect size) in VPM from baseline to 3 months post-treatment; and 2) adequate tolerability, defined as arm average participation in at least 80% of the treatment sessions. The duration associated with the highest arm average VPM at 3 months post-treatment, and also with adequate tolerability, will be selected.

The primary analysis will be intent-to-treat (ITT) and will model the change from baseline via a repeated measures linear mixed model which includes the following fixed effects: categorical visit (1 week, 3 months, and 6 months post-treatment period) by treatment arm (class variable) interaction, site, baseline aphasia severity score, and age. The estimated difference (95% confidence intervals) in change between each SET duration arm and control arm will be reported. The standardized mean difference for each SET duration versus control will be used to select the best dose of SET. The primary time point of interest is 3 months post-treatment, but the 1 week and 6 month post-treatment assessments will be explored to assess whether benefits are sustained over time. Since this study is not powered for direct comparison with control, no p-values will be reported.

Under the ITT principle, all participants who are randomized are included in the analysis. Therefore, missing data, especially in the primary outcome measure, can be problematic. All participants randomized will be included in the primary analysis regardless of whether or not they dropped out or discontinued treatment. For the primary analysis, a repeated measures linear mixed model will be fit; this is considered an implicit imputation approach if at least one post-baseline assessment is available. However, if baseline is the only assessment available (or if baseline is missing but follow-up available), then a nearest neighbor approach will be used to impute the missing values.

2.10.3. Confounders

Special care will be taken to evaluate the influence of potential confounders such as apraxia of speech, speech repetition scores, single word and sentence level comprehension [41]. As a sensitivity analysis, the primary analysis will be repeated while adjusting for these potential confounders to define determinants of the primary outcome. Since SET has not been systematically studied as a potential clinical treatment, the goal of SpARc is to determine if SET is associated with a robust effect size regardless of the underlying source of impairment, but it is very likely that cognitive and linguistic factors that vary across persons with non-fluent aphasia may influence SET outcome to different degrees. These variations and the overall benefit of SET will be explored by systematically assessing the effect size of SET and examining individual characteristics that relate to treatment response. This will be accomplished by assessing for interaction effects of potential confounders and treatment arm.

3. Discussion

3.1. SET vs control

For SET to be clinically useful, it has to be effective in comparison with a control, no SET condition, in which the individual with aphasia is followed and repeatedly tested but does not undergo a structured form of speech therapy. The control condition will provide an important benchmark against variability in speech production across time.

Based on our findings from our pilot data, those with chronic non-fluent aphasia who participated in SET achieved greater than 20% improvement in VPM during spontaneous speech at 3 months post-treatment. However, these findings were uncontrolled. Since individuals with chronic aphasia typically do not receive continuous speech therapy, we can likely assume that recovery of speech and language abilities is limited, if any at the chronic stage of recovery. Therefore, we would hope that comparing SET at any dose to no SET should show significant improvements in the treatment arm compared to minimal change in the control arm.

There is also the concept of learned nonuse that negatively affects speech and language ability in those with non-fluent aphasia, especially in the population with chronic aphasia. Learned nonuse implies that survivors of stroke tend to avoid using affected functions because doing so is inefficient, relying instead on the spared functions [42]. In the context of motor impairments, learned non-use is manifested by the preferential use of the spared limb, with little or no use of the paretic limb [43]. Although learned nonuse has not been frequently addressed in the aphasia literature, it is clear that there is a tendency for people with non-fluent aphasia to withdraw from communication situations. SET provides people with non-fluent aphasia as the result of a stroke with the opportunity to practice fluent speech and reverse some of the effects of learned nonuse in speech that will likely be seen in the control, no SET arm.

3.2. Optimal SET dose

One major question of this trial is what is the optimal dose of SET? We will compare the primary outcome, VPM, at 3 months post-treatment to select the best dose. Recommendations for clinical use will be determined by the optimal dose found. Since SET is a computerized therapeutic intervention, longer doses may be a feasible intervention if the technology is used in-home. This study will be an important addition to the literature supporting the efficacy of behavioral speech and language therapy for people in the chronic stages of aphasia.

3.3. Non-fluent aphasia and current treatments

Aphasia affects at least 20% of stroke survivors, and many individuals with aphasia persist with chronic language problems (>6 month after the stroke) [44]. Non-fluent aphasia specifically is common [45], strongly associated with lower quality of life [46], and notoriously difficult to treat. The majority of individuals with non-fluent aphasia do not achieve satisfactory gains in spontaneous speech with standard of care aphasia therapy [1,47] and this treatment gap constitutes an important and unmet clinical need, underscoring the importance of new and innovative forms of treatment.

This is a well-recognized area for improvement and past and current clinical trials have attempted to assess new approaches to treat non-fluent aphasia, including Constrained-Induced Aphasia Therapy (CIAT) [48] (ClinicalTrials.gov Identifier NCT00843427), Melodic Intonation Therapy [49] (NCT00903266), transcranial direct current stimulation (tDCS) (NCT01686373), tDCS coupled with Dextroamphetamine (NCT02514044) and transcranial magnetic stimulation (TMS) (NCT00608582, NCT02241213, NCT01512264). While these are promising new avenues of treatment, we believe that the therapy being proposed (SET) is unique and perhaps superior to other forms of therapy because it enables individuals with aphasia to practice relatively error-free fluent speech. SET guides the reestablishment of speech fluency, thus overcoming the initial barrier between non-fluent to fluent speech, which is not often observed with other therapies. SET has already been shown to significantly improve fluency from the preliminary trial, therefore continued research of this treatment in our proposed clinical trial is clinically relevant.

To the best of our knowledge, the only other form of therapy that induces relatively error-free speech is Melodic Intonation Therapy (MIT) [50,51]. In a small group study (n = 7), MIT was associated with increased number of correct information units in participants with non-fluent aphasia which was found to generalize to spontaneous speech [52]. However, MIT encourages verbal output with a prosody that is different from actual speech, and therefore less realistic.

If a best dose of SET is indeed selected, a future definitive clinical trial comparing SET with other forms of therapy would be pursued. During this future study, it will be paramount to determine the individual determinants of therapy success, not only to better inform clinicians, but also to evaluate the mechanisms associated with differential responses from SET versus other forms of therapy.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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