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BRIEF COMMUNICATION

Home-based biofeedback speech treatment improves dysarthria in repeat-expansion SCAs

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Abstract

CAG repeat-expansion spinocerebellar ataxias (CAG-SCAs) are genetically defined multisystemic degenerative diseases, resulting in motor symptoms including dysarthria with a substantial impact on daily living. Whilst speech therapy is widely recommended in ataxia, very limited evidence exists for its use. We evaluated the efficacy of a home-delivered, ataxia-tailored biofeedback-driven speech therapy in CAG-SCA in 16 individuals with SCA1, 2, 3, or 6. Treatment was delivered intensively over 20 days. Efficacy was evaluated by blinded ratings of intelligibility (primary) and acoustic measures (secondary) leveraging an intra-individual control design. Intelligibility improved post-treatment ($Z = -3.18$, $p = 0.004$) whilst remaining stable prior to treatment ($Z = 0.53$, $p = 1.00$).

Introduction

Spinocerebellar ataxias (SCA) are a group of autosomal-dominant neurodegenerative diseases that share progressive damage to the cerebellum and/or its associated cortical and spinal tracts, resulting in gait, balance and speech disturbance.[1] The most common SCAs are caused by CAG triplet repeat expansions (CAG-SCAs).[2] Dysarthria in SCAs can lead to significant declines in quality of life through social isolation, underemployment and difficulty completing daily tasks.[3]

Whilst speech therapy is recommended in clinical practice for ataxia, little evidence exists for degenerative ataxias,[4–6] with only single cases in SCAs.[4] A SCA-tailored speech treatment programme needs to cater to the physical, sensory and motor limitations of patients. The multisystemic phenotype and underlying progressive

neuropathology of repeat SCAs require that treatments are delivered intensively,[7,8] provide multi-sensory feedback (e.g. aural, visual) to maximize opportunities for self-monitoring, cater to the physical limitations of patients (i.e. home-based) and mitigates the adverse effect of clinical services that cannot offer intensive face-to-face treatment (i.e. delivered at home).

Here, we provide the first pilot, yet well-controlled evidence, for the efficacy of speech treatment in SCAs, thus exploring the effect of methods previously shown to be effective in a small patient cohort with certain autosomal-recessive ataxia (ARSACS)[5] to the most common SCAs.

Methods

Participants

Sixteen participants (aged 52.94 ± 13.90 years) with a genetically confirmed CAG repeat-expansion SCA (SCAs 1,2,3,6) were recruited (Table S1). Inclusion criteria were (1) age ≥ 18 years; (2) Scale for the Assessment and Rating of Ataxia (SARA)[9] total score >3, (3) SARA speech score ≥2, (4) ability to complete treatment protocol. All participants provided written informed consent. The study was registered ACTRN12616001582448 and received institutional approval in Germany (Az 003/2015BO2) and Australia (#1339394).

Treatment design

Treatment efficacy was tested via a rater-blinded intra-individually controlled trial. The training and assessment regime replicates procedures described in our proof-of-concept study in ARSACS.[5] Participants were assessed 4 weeks prior to speech treatment (A1), immediately prior to 4-week treatment (A2), and immediately after treatment (A3). Subjects acted as their own controls in a single-arm intra-individual control design whereby individual performance during the run-in phase prior to the intervention period (A1-A2) was compared to the intervention period (A2-A3). During treatment, subjects trained 45 min per day, 5 days per week, for 4 weeks, at home. Training and adherence to treatment were monitored through weekly telephone calls by a speech therapist.

Ataxia-tailored speech treatment exercises

Our speech phenotyping work in degenerative ataxia identified three broad areas of impairment requiring treatment[10,11]: i) intelligibility (ability to be understood); ii) vocal control; iii) prosody, (variation of duration, loudness, pitch). Therapy targeted these functions. Training task sets are described in Table S2.

Speech treatment software and biofeedback

Therapeutic methods were packaged into a home-based software program called Melbourne Ataxia Speech Treatment (MAST), with a simple interface for use on laptop PCs. MAST uses multi-sensory feedback (aural, visual, results in feedback (see Fig. 1a, video in Supplement)) to maximize opportunities for self-monitoring.

Outcome assessment

Speech samples were recorded using a laptop PC and a high-quality microphone. Participants completed four speech tasks at A1-A3, including an unprepared monologue, reading a passage, saying the days of the week and sustained vowel /a:/. All tasks were completed in a quiet room.

Primary outcome: intelligibility. Two blinded expert listeners (>15 years' dysarthria experience) randomized to subjects' assessment time-point (A1-A3) rated the monologue and reading passage using direct magnitude estimation (DME) described here.[5] DME uses a reference stimulus to represent "mild" dysarthria (scored 100). Higher scores indicate higher intelligibility. Improvement beyond 8.6% was considered clinically meaningful.[12]

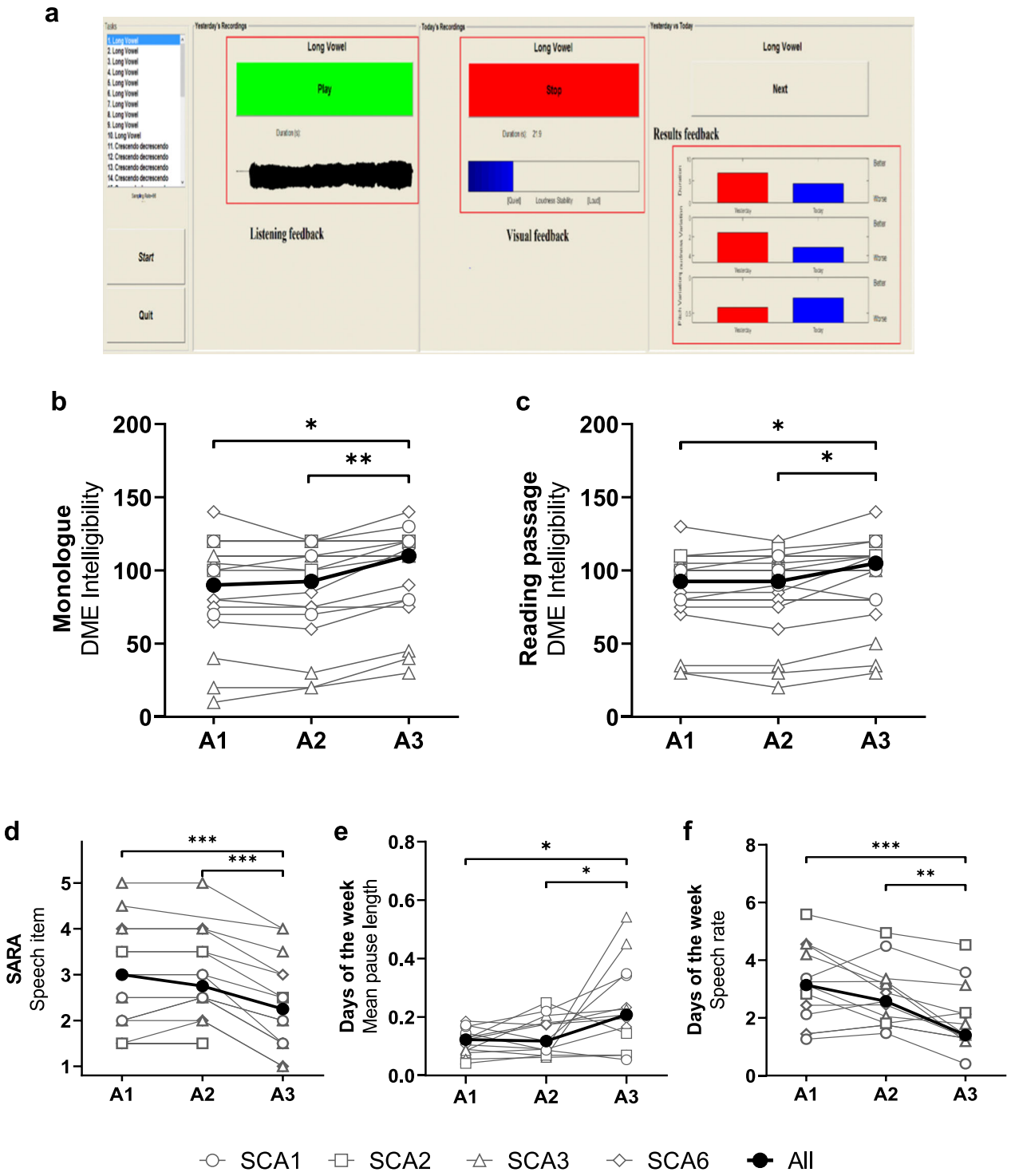
Secondary outcomes. Perceptual measures: The blinded same raters provided consensus ratings for prosody, respiration, phonation, resonance and articulation derived

Figure 1. Measures of speech intelligibility in response to speech rehabilitation. (A) Template of visual, aural and performance feedback during sustained vowel. Note: Three types of feedback were provided by the software program to drive the biofeedback-driven speech protocol: (i) Delayed next day listening feedback: Participants were prompted to record their speech each day. They then listened to their recorded sample from the previous day. This post-session listening feedback is important for the development of self-monitoring skills as it provides an opportunity for participants to hear their performance, identify what worked, what did not and set goals for the day; (ii) Real-time visual feedback: Visual feedback was provided through the real-time loudness and pitch displays. It allowed participants to monitor the stability or variability of their loudness and pitch whilst speaking. Variation in pitch and loudness was encouraged during connected speech tasks to reflect natural intonation during a conversation. Loudness and pitch were represented visually, providing additional feedback to listening, maximizing opportunities for improvement; (iii) Delayed at-end-of-task results feedback: After completion of the task-set, participants were provided objective feedback on whether their speech was better or worse than the previous day's production. Measures of speech intelligibility in monologue (B) and reading passage (C) in response to speech rehabilitation. The largest gains were observed in SCA6 (see also Fig. S1A,B). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; (D) SARA speech item in response to speech rehabilitation, Figure 2. Acoustic measures of speech timing (E-F) in response to speech rehabilitation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; DME: Direct magnitude estimation.

from the monologue and vowel, using a 5-point severity scale (0–4: 0 = unremarkable, 4 = severe).

Objective digital measures. Acoustic features of timing (e.g. pause length), vocal control (e.g. frequency variation) and voice quality were acquired using purpose-built algorithms for MATLAB and PRAAT software.[13,14]

Non-parametric analyses were applied to perceptual data. A linear mixed-effects model analysis with restricted maximum likelihood estimation was applied to acoustic features which account for missing data by modelling the random effects. An adjusted significance level was set using a two-stage procedure for controlling



the false discovery rate,[15] or Bonferroni correction when appropriate.

Results

Primary outcome—intelligibility

Intelligibility significantly improved between assessments ($\chi^2(2) = 16.55$, $p < 0.001$; Figure 1b), remaining stable during run-in (A1-A2: Z = 0.53, $p = 1.00$), but increasing during treatment (A2-A3: Z = -3.18, $p = 0.004$). The median change in the intelligibility of monologue was 10% (range 0–30%; Fig. S1a). At a single-subject level, 12/16 subjects responded to treatment. Changes seen in intelligibility post-speech treatment did not lead to improved naturalness on the monologue ($\chi^2(2) = 0.05$, $p = 0.98$) or reading tasks ($\chi^2(2) = 4.04$, $p = 0.13$). SCA variants did not differ statistically in their response.

Secondary outcomes

SARA speech item improved with treatment (A2-A3: T = 3.97, $p = 0.002$; Fig. 1d), whilst remaining unchanged prior to treatment (A1-A2: T = 0.66, $p = 0.52$). Pitch (T = 4.43, $p = 0.003$) and loudness variability (T = 2.74, $p = 0.03$), strain/strangled voice quality (T = 3.48, $p = 0.006$) and consonant pronunciation (T = 3.48, $p = 0.006$) all improved with treatment (A2-A3), whilst remaining unchanged prior to treatment (A1-A2) (Table S4.) Acoustically, intelligibility improved with treatment (Fig. S2), mean pause length increased (A3; $p = 0.01$; Fig. 1e) and speech rate decreased (A3; $p < 0.001$; Fig. 1f) with treatment (Table S4).

Determinants of benefit from speech therapy

Improvements in intelligibility, SARA speech and speech rate did not correlate with disease severity, duration or age of onset (Table S5). Intelligibility for the reading task positively correlated with disease duration (r (15)=0.61, $p = 0.02$; Figure 2a). Mean pause length correlated with disease severity (SARA; r (11)=0.60, $p = 0.03$; Figure 2b).

Discussion

Speech treatment might be effective in SCAs: First pilot evidence

Dysarthria eventually impacts all individuals with SCA. Whilst speech therapy is widely recommended as part of SCA treatment,[16] evidence for its efficacy is missing. Accessible, evidence-based ataxia-tailored therapies are needed to improve communication-related health and quality of life. The Melbourne Ataxia Speech Treatment (MAST) provides tailored feedback and stimuli designed to enhance speech clarity, voice quality and vocal control. The software harnesses advances in technology to bring therapy to the user's home whilst allowing remote monitoring of adherence and performance by the clinician.

The findings from our intra-individually controlled run-in, rater-blinded, 4-week home-based treatment trial suggest the biofeedback-driven approach to improve speech intelligibility for the majority (75%) of SCA subjects treated. These results validate and extend the findings of earlier work on feedback-based speech therapy in

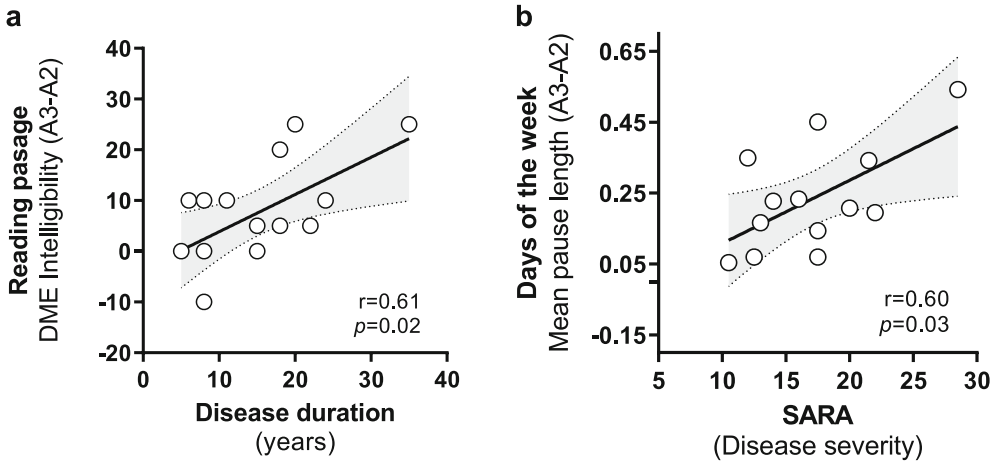


Figure 2. The relationship between measures sensitive to change in the speech rehabilitation intervention and disease severity and duration. Gray shaded area represents 95% confidence intervals. Figures include change scores of A2-A3 (n = 14). N = 2 participants with missing data due to corrupted file recordings on Days and Reading tasks.

case series of multisystemic early-onset ataxia (ARSACS).[5] Significant improvements in intelligibility (*a priori* primary outcome measure analyzed by two blinded raters) across all disease groups were observed, with the largest gains found in SCA6. This group effect was validated on an individual subject level, with 12 of 16 subjects (75%) demonstrating increases in intelligibility equal to or greater than 10 points. The effectiveness of speech therapy did not appear to be dependent on baseline dysarthria severity, with both mild and moderately affected subjects showing treatment effects (see Fig. 1d, also note the lack of correlation between SARA speech item and treatment benefit).

Possible speech mechanisms underlying effective speech therapy

Our study provides the first insight into the mechanisms underlying the benefits of speech therapy in SCAs. Specifically, our perceptual data suggest that improvements in intelligibility were driven by changes in vocal control (reduced variability in pitch and loudness), voice quality (reduced strain/strangle) and enhanced consonant precision. Acoustically, we observed reductions in speech rate and mean pause length post-treatment suggesting that speakers reduce their overall rate and increase the length of gaps between words to maximize opportunities for clear speech.

Subjects were instructed to 'over enunciate' and produce speech clearly. They were also supported to improve their breath support and develop greater vocal control on sustained vowel tasks via the three feedback approaches (aural, visual, performance). Slowing speech rate likely provided speakers more time for accurate production of consonants, alongside improvements in voice quality and vocal control. All elements combined appear to result in speech that is easier to understand for the listener.

Limitations of the study

Although sufficiently sized to see changes in primary (and secondary) outcomes, the sample size remains small and requires further validation. We did not include a control group with active therapy for head-to-head comparison (i.e. single arm), but controlled for this limitation by including an intra-individual study design. Based on the larger gains observed in the SCA6 participants, future treatment studies could focus on specific genotypes (i.e. one CAG-repeat SCA) to strategically isolate mechanisms of change by the group. We did not measure the long-term effectiveness of therapy, making exploration of the enduring impacts of treatment an important goal.

Conclusions

The study provides the first evidence that speech therapy is effective in repeat-expansion SCAs. At the same time, it suggests that home-delivered biofeedback therapy is a promising approach—an important feature for rare disease patients who are often distributed geographically without direct access to skilled therapists. We have validated and extended earlier work in ultra-rare ARSACS[5] to the most common hereditary ataxias (SCAs). This provides world-first evidence of speech therapy in SCAs and makes the key step before embarking on a larger multicenter randomized controlled trial.

Author Contributions

Prof Vogel conceived the study, designed the treatment, contributed to the design of the study, collection, analysis and interpretation of the data and drafting the manuscript. He also supervised students, led the research team and obtained funding for the research. Ms. Lisa Stoll contributed to data analysis and interpretation and revising the manuscript for intellectual content. Dr Magee contributed to data analysis and interpretation and revising the manuscript for intellectual content. Prof Schöls contributed to data interpretation and revising the manuscript for intellectual content. Ms. Rommel contributed to the design of the study, collected data, analysis and interpretation of the data, revising the manuscript for intellectual content and supervision of students. Prof Synofzik contributed to the design of the study, collection, analysis, and interpretation of the data, and revising the manuscript for intellectual content. He also supervised students, led the research team, and obtained funding for the research.

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Conflicts of Interest

Prof Vogel and Dr Magee are employees of Redenlab Inc, a speech neuroscience company. They also receive institutional support from The University of Melbourne. Ms. Rommel and Ms. Stoll all have no conflict of interest. Prof Dr Schöls receives funding from the German Research Foundation (DFG), the European Union and

the German Hereditary Spastic Paraplegia Foundation unrelated to this study. Dr Synofzik received honoraria from Orphazyme Pharmaceuticals, Janssen Pharmaceuticals, AviadoBio and Ionis Pharmaceuticals, all unrelated to the current study.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 Genotype-specific differences in speech intelligibility (a-c) and acoustic measures of speech timing (e-f) in response to speech rehabilitation. Note: N = 2 participants with missing data due to corrupted file recordings on Days and Reading tasks. DME = direct magnitude estimation. A2 = Assessment directly before treatment. A3 = Assessment directly after assessment.
Figure S2. Objective digital outcomes of treatment. Averaged baselines (A1-A2) versus post-treatment.
Table S1. Clinical and demographic characteristics for patient cohort at baseline (A1).
Table S2. Components of therapy design.
Table S3. Perceptual (expert listener-based) analysis of speech to measure the effectiveness of an intensive speech rehabilitation in SCA.
Table S4. Acoustic features of speech to measure the effectiveness of an intensive speech rehabilitation in SCA.
Table S5. The relationship between measures sensitive to change in the speech rehabilitation intervention and disease severity, duration, and age of onset.

