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ORIGINAL COMMUNICATION

Speech treatment improves dysarthria in multisystemic ataxia: a rater-blinded, controlled pilot-study in ARSACS

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Abstract

We aimed to provide proof-of-principle evidence that intensive home-based speech treatment can improve dysarthria in complex multisystemic degenerative ataxias, exemplified by autosomal recessive spastic ataxia Charlevoix-Saguenay (ARSACS). Feasibility and piloting efficacy of speech training specifically tailored to cerebellar dysarthria was examined through a 4-week program in seven patients with rater-blinded assessment of intelligibility (primary outcome) and naturalness and acoustic measures of speech (secondary outcomes) performed 4 weeks before, immediately prior to, and directly after training (intraindividual control design). Speech intelligibility and naturalness improved post treatment. This provides piloting evidence that ataxia-tailored speech treatment might be effective in degenerative cerebellar disease.

Keywords Speech · Dysarthria · Rehabilitation · Acoustics · Ataxic neuropathy · Voice

Introduction

Evidence-based strategies to treat dysarthria in degenerative spinocerebellar ataxias are absent [13]. Treatment is in particular challenging in multisystemic ataxia disorders, like autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), where complex co-morbid damage to extracerebellar neural systems places additional disease burden on the ataxia patients, including pyramidal, visual, cognitive, and peripheral nerve damage [9].

Here we hypothesized that intensive, home-based biofeedback-driven training with exercises designed to enhance neuroplasticity and motor learning might improve speech in multisystemic degenerative spinocerebellar ataxias, taking ARSACS as a paradigmatic example in a piloting proof-of-concept study. The study employed a rater-blinded intraindividual control design to evaluate the efficacy of ataxia-tailored speech exercises delivered through portable digital devices in patients' homes.

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Methods

Participants

Seven individuals with genetically confirmed ARSACS were recruited from two sites, the Department of Neurology, University Hospital Tübingen, Germany and Alfred Health, Melbourne Australia. Participants met the following inclusion criteria: (1) genetically confirmed ARSACS; (2) age > 17 years; (3) Scale for the Assessment and Rating of Ataxia (SARA) [8] total score > 3 and speech subscore ≥ 2. For basic characterization, participants underwent a standardized neurological examination for ataxia severity [SARA [8]), cognition (Montreal Cognitive Assessment, (MoCA)] [5] and Activities of Daily Living [4] (see Table 1 participant details). Training was completed in German for the German participants and English for the Australian participant.

All participants or their legal representative provided written informed consent prior to participation. The study received institutional ethical approval (The University of Melbourne 1339394.2, University Hospital Tübingen, Germany Az. 003/2015BO2). The trial was registered with ID ACTRN12616001583437 (anzctr.org.au).

Study design

We evaluated the efficacy of a rater-blinded delayed-entry 4-week home-based treatment trial. Participants were assessed three times during the trial: 4 weeks prior to training (A1), immediately before training (A2), and immediately after training (A3). To control for the potential effect of treatment as well as individual variability and repeated assessments, participants acted as their own controls in an intra-individual control design whereby their performance during the non-treatment period (A1–A2) was compared to their treatment period (A2–A3). Participants did not receive any speech therapy between A1–A2. During the intervention period, subjects trained about 45 min per day, 5 days per week, for 4 weeks at their homes. Training was monitored by weekly telephone calls by a speech therapist.

Ataxia-tailored speech treatment protocol

Speech deficits in ARSACS affect intelligibility, vocal control, and prosody (appropriate manipulation of duration, loudness, and pitch) [15]. Therapeutic strategies were selected and combined to target these three functions (see Table 2 for components of therapy design). Treatment

Table 1 Clinical and demographic details of participants with ARSACS

Participant	1	2	3	4	5	6	7
Sex	Male	Female	Female	Male	Female	Female	Female
Education, y	11	9	9	12	14	9	12
Age at onset, y	4	27	11	4	3	25	26
Disease duration, y	24	21	22	22	46	33	2
Nucleotide and amino acid exchange allele 1	c.2182C > T | p.Arg728*	c.2881C> | p.Arg961*	c.9305_9306insT | p.Leu3102Phefs*8	c.4076 T > G | p.Met1359Arg	c.4954C > T | p.Gln1652*	c.4774G > A | p.Asp1582Asn	c.3352dupT | p.Cys1118fs*3
Nucleotide & amino acid exchange allele 2	c.10651dupA | p.Met35551Asnfs*4	c.4756_4760del | p. 1586_1587del	c.9305_9306insT | p.Leu3102Phefs*8	c.4076 T > G | p.Met1359Arg	c.5125C > T | p.Gln1709*	c.10686_10689 del | p.Phe3562Leu_fs*8	c.10550T > G | p.Leu3517Arg
Ataxia severity (SARA)[#]	19.5	20	17	18	23	33	22.5
SARA speech item	2	2	2	2	2	3.5	2
MoCA at baseline[a]	21	24	17	27	24	23	~
IADL at baseline[a]	7	5	5	6	4.5	4	6

Missing data; *y* years, *IADL* Instrumental Activities of Daily Living, *SARA* Scale for the Assessment and Rating of Ataxia where mean SARA score of healthy controls is 0.4 ± 1.1 (range 0–7.5) (Schmitz-Hubsch et al. 2006), *MoCA* Montreal Cognitive Assessment

[a]Higher values indicate better performance

[#]Lower values indicate better performance

Table 2 Components of therapy design

Stimuli	Daily tasks: (i) words and sentences [a]; (ii) long vowel x 10 repetitions [b]; (iii) loudness and pitch control exercises x 10 each [b]; (iv) short phrases with target word designed to improve prosody x 15 [c]; (v) reading task [a–c]; (vi) transfer exercise (daily question) [a–c]
Elicitation method	Imitation of clinician's production in first session and on weekly calls, then reading stimuli on PCs for non-supervised sessions
Treatment trials	Per goal: 30–40 trials; total trials per session: 120. Session duration: 30–45 min
Teaching strategies/cues	Initial session and weekly follow-up: verbal instructions, modelling and training on interpretation of feedback
Feedback	Aural and visual via biofeedback and knowledge of results via acoustic outcomes of duration, pitch and loudness variation

Treatment goals [a]Intelligibility, [b]vocal control, [c]prosody

Intelligibility was targeted by prompting participants to spontaneously modify their habitual speech via rate reduction and purposeful articulation (over-enunciation) [7, 8]. Prosody was improved by requiring participants to produce meaningful prosodic contrasts at the word and phrase level in set phrases, an approach that has been successfully applied to related populations such as Parkinson's disease and post-stroke [9, 10]. Vocal control was trained by eliciting repeated maximum phonation time tasks, pitch glides and crescendos, prompting participants to focus on accurate coordination of respiratory and phonatory systems [11]

strategies and a description of modes and timing of feedback provided during treatment are described below.

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 provided an opportunity for participants to hear their performance, identify what worked, and set goals for the day.

Real-time visual feedback

Visual feedback was provided through the real-time loudness and pitch displays. Participants monitored the stability or variability of their loudness and pitch while speaking. Similarly, variation in pitch and loudness was encouraged during connected speech tasks to reflect natural intonation during conversation. Loudness and pitch were represented visually, providing additional feedback to listening, maximising opportunities for improvement.

Delayed (at end of task) results feedback

Participants were provided objective feedback on whether their speech was better or worse than the previous day's production. Three pieces of information were derived from the recorded samples: (i) duration, which is important for the long-vowel task; (ii) loudness variation and (iii) pitch variation, both important for improving vocal control and intonation in the vowel and connected tasks, respectively. This information was designed to enhance the patient's perception of their speech and to provide a benchmark against which to compare earlier productions. Summary figures were provided at the end of each day. The clinician could plot/track their patients' progress—highlighting gains made during therapy as well as adherence to treatment.

Treatment methodology

These therapeutic methods have been packaged into a home-based treatment software program called Melbourne Ataxia Speech Treatment (MAST) with a simple user interface suitable for use on laptop PCs provided to the patient. *MAST* uses multi-sensory feedback—both aural, visual and results feedback (self-comparison) (see Fig. 1 and video in Supplementary Materials)—to maximise opportunities for self-monitoring. The multiple biofeedback modalities are designed to focus the speaker on external controls of speech, thus enhancing their own monitoring of production.

Outcome measures

Primary outcome measure

A blinded listener-derived rating of speech intelligibility. Two expert raters (> 15 years' experience working with dysarthria) listened to speech files recorded at A1, A2 and A3, presented in a randomized order with raters blinded to assessment time point. Intelligibility was rated via expert perceptual judgement of the first 30 s from the monologue using direct magnitude estimation (DME) [16]. DME is a means of standardising subjective listener judgments. The technique is used with a reference stimulus chosen by consensus of experts as a good exemplar of "mild" dysarthria (given a score of 100). The raters then assigned values greater than 100 to denote better performance on measures of intelligibility. For these parameters, a value of 200 indicates that a sample is rated twice as good as the reference sample, while a value of 50 denotes the sample is only half as intelligible compared with the reference. DME

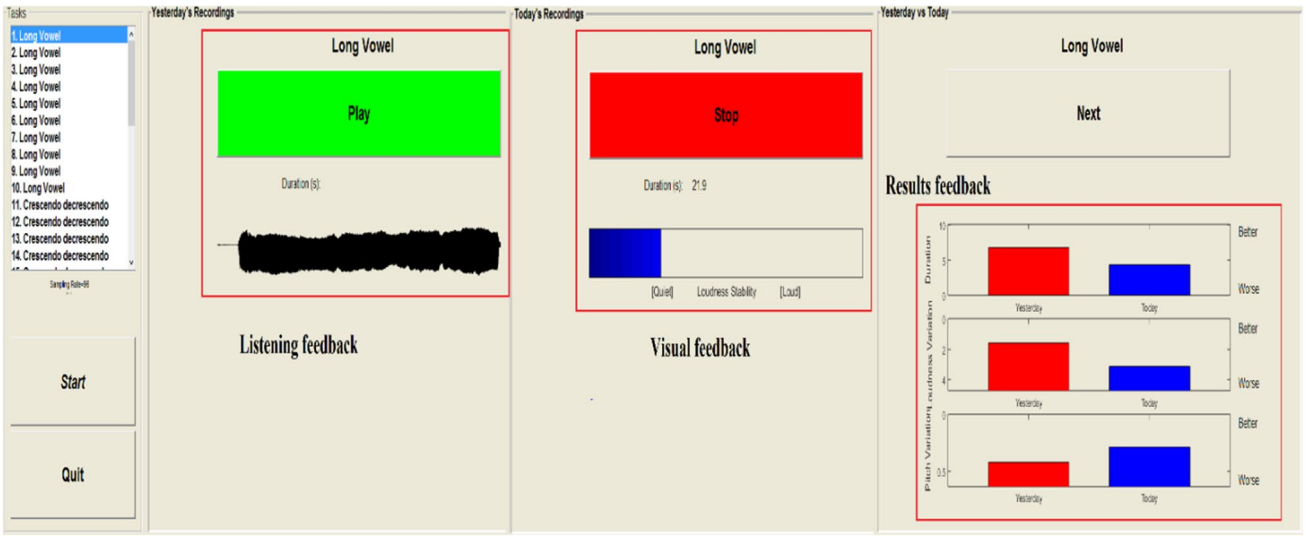

Fig. 1 Melbourne Ataxia Speech Treatment (MAST): example of long vowel task

was considered more accurate and reliable than standard severity ratings [7] for determining change.

Secondary outcome measures

A subset of objective acoustic measures and subjective (listener-based) measures of speech were used to measure change between time points. These variables were selected from earlier work describing differences between healthy controls and individuals with ARSACS [15]. Acoustic [measures of timing (e.g. mean and variability of pause length) and vocal control (e.g. variability of fundamental frequency)] and perceptual measures: pitch breaks, prolonged intervals, equal and excess stress, imprecise consonants, vowel distortion, intelligibility and naturalness, were used.

Acoustic and listener-based outcomes were derived from the following speech stimuli: (a) reading a brief phonetically balanced passage; (b) prolonged production of vowels: sustain an open "ah" vowel for as long as possible; (c) monologue: for one minute on selected topics (e.g. current physical functioning). These tasks and corresponding acoustic outcome measures have demonstrated reliability, stability and sensitivity to change [12]. The battery has been adapted and validated in German [14] and takes < 6 min to elicit. Speech was recorded using a high-quality microphone (AKG C520 condenser microphone, AKG Acoustics GmbH, Vienna, Austria), an external sound card (QUAD-CAPTURE USB 2.0 Audio Interface, Roland Corporation, Shizuoka, Japan) and a laptop PC. Testing was conducted in a quiet room free from environmental noise.

Statistical methods

Analyses were performed using the non-parametric Friedman test ($\chi 2$, p-values) to determine within group differences between A1-A3. When the Friedman test yielded a significant effect ($p < 0.05$), post hoc analysis was performed using a Wilcoxon signed-rank test for pair-wise comparisons between assessments with a significance level $\alpha = 0.05$. Spearman's rho was used to examine the associations between SARA scores and intelligibility. Intra-class correlation (ICC) and corresponding confidence intervals (CI) was used to examine inter-rater reliability. In case of disagreement, the more conservative assessment (i.e. the lower DME value) was adopted for final judgement.

Statistical analysis was performed using the software package SPSS 22.

Results

ICC of perceptual scores between raters was 0.835 (95% CI = 0.91–0.701) ($p < .001$). Mean (SD) intelligibility at baseline (A1) was 117.1 (± 19.3) points as determined by DME, equalling a relatively mild overall dysarthria in this ARSACS cohort, despite an advanced overall ataxia stage (average SARA score 21.9 ± 5.4 points). All 7/7 subjects completed the training, indicating feasibility and acceptability of our speech treatment protocol. Intelligibility of monologue changed between the three assessments ($\chi^2 = 8.67$, $p = 0.013$; Friedman test). While the DME score remained unchanged before training (A1/A2: Z = 4.0, p = 0.71; Wilcoxon's signed-rank test), it increased significantly to 128.8 (± 14.6) after treatment (A2/A3: $Z = 21.0$, $p = 0.024$; see

Fig. 2; for ratings of all speech domains, see Supplements 1 and 2). Individual relative changes in intelligibility varied between minus 7 and 33%. On an individual level, 57% (4/7) patients responded to treatment, defined as baseline to post-treatment intelligibility improvement of ≥ 10%. This number increased to 6/7 if a positive change from baseline was used to indicate improvement. Significant increases in naturalness were also observed across the three timepoints ($\chi^2 = 6.08$, $p = .048$; Friedman test) and between A2/A3 (Z=-2.232, $p = .026$).

Overall SARA scores at baseline were significantly correlated with the size of improvement (change) in intelligibility on the reading task ($\rho = -0.926$, $p = .003$), but not intelligibility of the monologue or either naturalness score. Speech severity at baseline was not related to the change in intelligibility or naturalness post treatment.

There were no statistically observable changes in specific measures of prosody, voice quality or control beyond those reported within the wholistic measures of intelligibility and naturalness, and no significant differences in acoustic measures (Supplement 3).

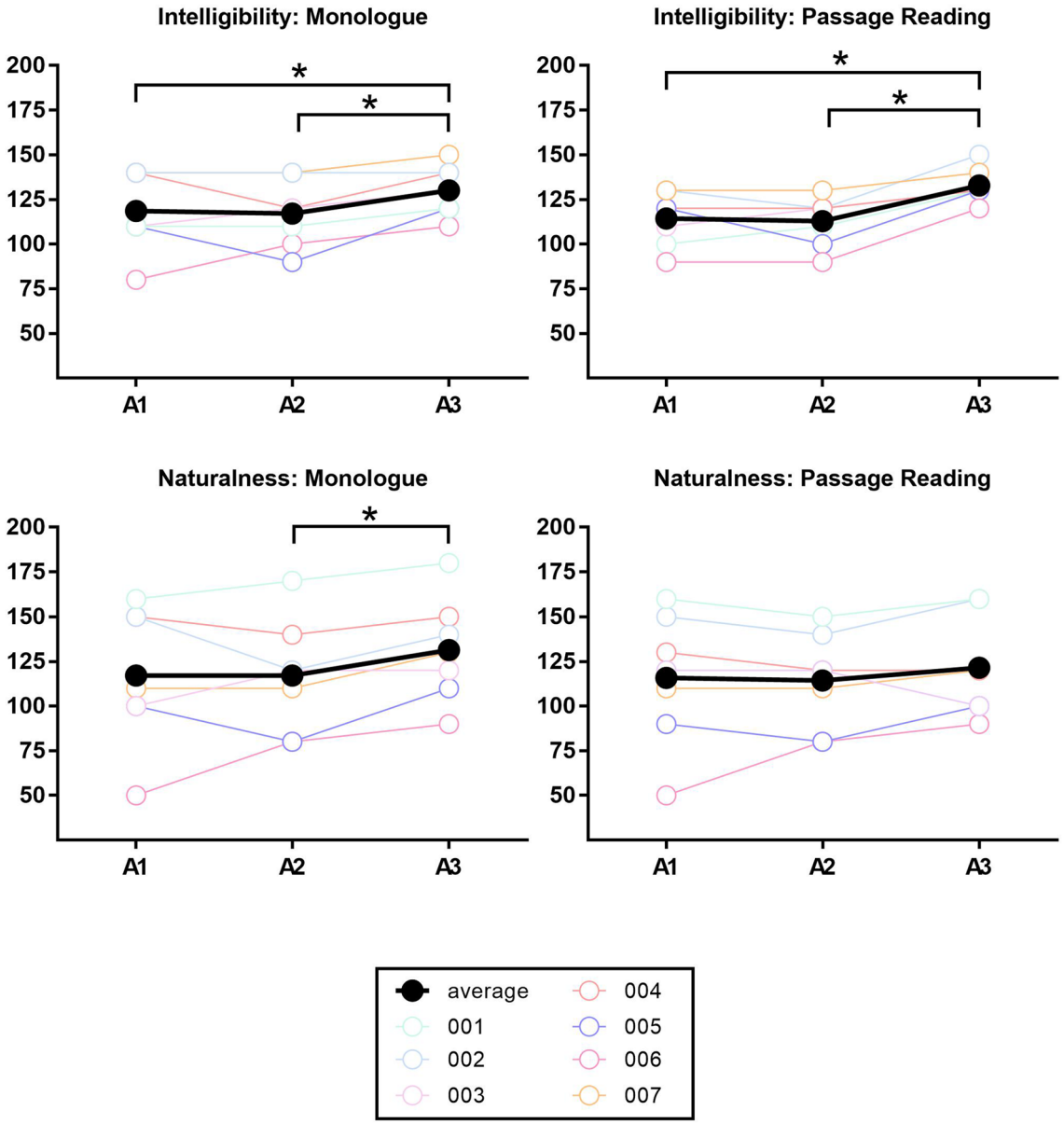

Fig. 2 Intelligibility and naturalness at baseline/s and post-treatment about here

Discussion

These findings deliver preliminary proof-of-concept evidence on different levels: we observed (1) feasibility of the speech treatment protocol (100% completion rate), (2) improvements in intelligibility (ability to be understood) during connected speech tasks; and (3) enhanced naturalness (degree to which individuals sound 'different' from healthy peers). Importantly, we observed large clinically significant improvements in more than half of the participants, as improvements in intelligibility post training of > 10% (Fig. 1) indicates a clinically meaningful change (given that relative improvements in intelligibility of 5–10% represent perceivable changes in output [2]).

These changes are noteworthy as the judgments were conducted by blinded raters, and that baseline severity levels of dysarthria were mild (DME 117 points), showing that even relatively low levels of impairment are ameliorable to treatment. Moreover, given the intra-individual control design, with no changes observed during the pre-treatment baseline period (A1–A2), we can rule out changes occurring simply through repeated assessments or variability in disease course.

The treatment was designed to fulfil several criteria which make it an attractive treatment option for ataxia patients: it incorporated multi-sensory feedback (e.g. aural, visual) to maximise opportunities for self-monitoring; it catered to the physical limitations of ataxia patients (i.e. home-based, large visual display); it mitigated the adverse effect of clinical services that cannot offer intensive face-to-face treatment; it is adaptable for use in ataxia patients with comorbid damage of other neuronal systems; and it enabled completion at home, enhancing patient autonomy.

Limitations

The study is limited by the small sample size, yet it was designed to provide only first piloting proof-of-concept evidence. Moreover, it bears the advantage that it included only ataxia patients with one (ultra-rare) genetically defined ataxia type (ARSACS), rather than including a mixture of different genetic ataxia diseases, thus allowing evaluation of a homogeneous, gene-defined patient cohort. Our study is limited by the lack of sham training, yet it did include control for an absence of the target treatment, exploiting an intra-individual control study design. Finally, we did not assess longer term outcome measures beyond immediately post treatment. Meeting these challenges in a larger randomized controlled trial as well as in other degenerative ataxias will be a priority for future work.

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Author contributions AV designed the treatment and 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. LS contributed to data analysis and interpretation and revising the manuscript for intellectual content. AO contributed to data analysis and interpretation and revising the manuscript for intellectual content. E-MK contributed to data analysis and interpretation and revising the manuscript for intellectual content. DS contributed to therapy material preparation and revising the manuscript for intellectual content. CA contributed to therapy material preparation and revising the manuscript for intellectual content. NR 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. LS, DT and ES contributed to data interpretation and revising the manuscript for intellectual content. MS 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.

Compliance with ethical standards

Conflicts of interest All authors declare that they have no conflict of interest.

Ethical standards The study received institutional ethical approval (The University of Melbourne 1339394.2, University Hospital Tübingen, Germany Az. 003/2015BO2). The trial was registered with ID ACTRN12616001583437 (anzctr.org.au).

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