# Features of speech and swallowing dysfunction in pre-ataxic Spinocerebellar Ataxia Type 2

Adam P. Vogel [1, 2, 3] (PhD), Michelle Magee [1] (PhD), Reidenis Torres Vega [4] (MSc), Jacqueline Medrano-Montero [4] (DSc), Melissa P Cyngler [1] (MSc), Megan Kruse [1] (MSc), Sandra Rojas (MSc) [1], Sebastian Contreras Cubillos [5,6] (MSc), Tamara Canento [1] (MD), Fernanda Maldonado [1] (BSc), Yaimee Vazquez-Mojena [4] (BSc), Winfried Ilg [2,8] (PhD), Roberto Rodríguez-Labrada [4] (PhD), Luis Velázquez-Pérez [4 *] (MD, PhD), Matthis Synofzik[2,8 *] (MD).

[1] Centre for Neuroscience of Speech, The University of Melbourne, Victoria, Australia
[2] Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen, Germany & Center for Neurology, University Hospital Tübingen, Germany
[3] Redenlab, Australia
[4] Center for Research and Rehabilitation of Hereditary Ataxias (CIRAH), Holguin, Cuba
[5] University of Santo Tomas, Talca-Chile
[6] Escuela de Fonoaudiologia, Facultad de Salud, Universidad Santo Tomas, Chile;
[7] Physical Medicine & Rehabilitation Service, Speech Therapy Unit, Hospital of Curico-Chile.
[8] German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany
* joint senior authors

| | |
|---|---|
| Title character count: | 89 |
| Manuscript word count: | 3,100 |
| Abstract word count: | 225 |
| Number of references: | 46 |
| Number of figures: | 5 |
| Number of tables: | 2 |

**Corresponding author:**
Adam Vogel PhD
Centre for Neuroscience of Speech
The University of Melbourne
550 Swanston Street, Parkville
Melbourne VIC 3010, Australia
Phone: +61 3 9035 5334
Email: vogela@unimelb.edu.au

**Keywords:** speech, dysarthria, acoustics, dysphagia, swallowing, pre-symptomatic, ataxic neuropathy, degenerative ataxia

**Running title:** Speech timing and swallowing function in early SCA2

## FINANCIAL DISCLOSURES:

Dr. Adam P. Vogel (PhD) received salaried support from the National Health and Medical Research Council, Australia (Career Development Fellowship ID 1082910), and received funding from the Alexander von Humboldt Foundation and serves as the Chief Science Officer of Redenlab Pty Ltd.

Dr. Michelle Magee (PhD) reports no disclosures

Mr. Reidenis Torres Vega (MSc) reports no disclosures

Dr. Jacqueline Medrano-Montero (DSc), reports no disclosures

Ms. Melissa P Cyngler (MSc) reports no disclosures

Ms. Megan Kruse (MSc) reports no disclosures

Ms. Sandra Rojas (MSc) reports no disclosures

Mr. Sebastian Contreras Cubillos (MSc) reports no disclosures

Dr. Tamara Canento (MD) reports no disclosures

Ms. Fernanda Maldonado (BSc) reports no disclosures

Ms. Yaimee Vazquez-Mojena (BSc) reports no disclosures

Dr. Winfried Ilg (PhD) reports no disclosures

Dr. Roberto Rodríguez-Labrada (PhD) reports no disclosures

Dr. Luis Velázquez-Pérez (MD, PhD) reports no disclosures

Dr. Matthis Synofzik (MD) has received speakers' honoraria from Actelion Pharmaceuticals and the Movement Disorders Society, both unrelated to the current study.

**Statistical Analysis** was conducted by Dr. Michelle Magee, PhD, Centre for Neuroscience of Speech, The University of Melbourne, Victoria, Australia

**This study was funded** by the Center for Rare Diseases Tübingen (ZSE Tübingen; to Dr. Matthis Synofzik and Dr. Adam P. Vogel). The Cuban Ministry of Health provided institutional support to Luis Velázquez-Pérez.

**ABSTRACT:**

**Objective:** To determine if objective and quantitative assessment of dysarthria and dysphagia in SCA2, specifically at pre-ataxic and early disease phases, can act as sensitive disease markers.

**Methods:** Forty-six individuals (16 pre-ataxic SCA2, 14 early-stage ataxic SCA2 and 16 healthy controls) were recruited in Holguin, Cuba. All participants underwent a comprehensive battery of assessments including objective acoustic analysis, clinician derived ratings of speech function and swallowing, and quality of life assessments of swallowing.

**Results:** Reduced speech agility manifest at the pre-ataxic stage was observed during diadochokinetic tasks, with the magnitude of speech deficit augmented in the early-ataxic stage. Speech rate was slower in early-stage ataxic SCA2 compared with pre-ataxic SCA2 and healthy controls. Reduced speech agility and speech rate correlated with disease severity and time to ataxia onset, verifying speech deficits occurred prior to ataxia onset and increase in severity as the disease progresses. Whilst dysphagia was observed in both pre-ataxic and ataxic SCA2, it was not associated with swallowing-related quality of life, disease severity or time to ataxia onset.

**Conclusions:** Speech and swallowing deficits appear sensitive to disease progression in early-stage SCA2, with syllabic rate a viable marker. Findings provide insight into mechanisms of disease progression in early-stage SCA2 signalling an opportunity for stratifying early-stage SCA2 patients and identifying salient markers of disease onset as well as outcome measures in future early-stage therapeutic studies.

**INTRODUCTION:**

Spinocerebellar ataxia type 2 (SCA2) is one of the most common hereditary ataxias, accounting for 13–18% of dominant ataxias worldwide [1, 2]. SCA2 is caused by an abnormal expansion of the trinucleotide Cytosine–Adenine–Guanine (CAG) repeat within the coding region of the ataxin-2 (ATXN-2) gene (12q23-24.1) [3-5]. This leads to expression of the long polyglutamine sequence in the Ataxin-2 protein [6] causing dysfunction and death of neurons in the cerebellum, brainstem, spinal cord, and brain cortex [7, 8]. SCA2 typically manifests in a broad range of progressive features such as gait ataxia [9], dysarthria [10, 11], dysmetria, oculomotor disturbances [12, 13], hyporeflexia, cerebellar tremor, parkinsonism [14] and cognitive dysfunctions [15].

Dysarthria is commonly associated with cerebellar disease progression [16-18], however, the severity and impact are still poorly characterised in SCA2. A small number of cases series (with limited participant numbers and mixed SCA genotypes) have characterised the speech of individuals with ataxic SCA2 as breathy, hoarse, and strained-strangled vocal quality, slow speech rate, reduced diadochokinetic rate, increased pause durations and increased vocal instability [10, 18, 19]. A similar level of evidence is available for describing the swallowing profile in SCA2. Some reports describe oropharyngeal dysphagia leading to malnutrition, dehydration and aspiration pneumonia, which can be fatal [20-22].

Quantitative information on the disease course of the speech and swallowing phenotype is missing completely for the pre-ataxic disease stage of SCA2, where it could aid to individually stratify this unique time window for preventive therapies. The autosomal-dominant inheritance pattern of SCA2 makes it an ideal candidate population to explore how dysarthria and dysphagia - as two cardinal features of spinocerebellar degeneration - manifest across the disease course. Earlier reports of pre-ataxic SCA2 suggest that individuals may experience muscle cramps, hyperreflexia, sensory deficits, oculomotor disturbances, changes in gait, visual memory impairments, executive function deficits and autonomic dysfunction[23-25].

Tracking behaviours from the pre-ataxic stage through to manifestation of ataxia disease at early stages, may provide useful data on how individuals adapt to changes in function, the relative timing of these changes, and the importance of identifying specific deficits and markers to individually stratify across disease stages. Of particular interest is the ‘conversion stage’ given the potential to target this period in future disease-modifying therapies.

Here we present a comprehensive study of speech and swallowing function in pre-ataxic to early-stage ataxic SCA2 individuals, using objective measures of speech combined with detailed measures of swallowing and quality of life.

## METHODS:

### *Participants*

Sixteen pre-ataxic SCA2 mutation carriers (aged 39.0 ± 8.9 years, 5M, 11F, CAG repeat range; 34 to 41, Scale for the Assessment and Rating of Ataxia [SARA]: 0.59 ± 0.69), 14 ataxic SCA2 mutation carriers at early stage (aged 37.8 ± 10.6 years, 7M, 7F, CAG repeat range; 36 to 44; disease duration: 3.79 ± 3.75 years, SARA: 6.14 ± 2.18) and 16 healthy controls matched for age and sex (aged 38.4 ± 10.5 years, 7M, 9F)) were recruited from the Centre for Research and Rehabilitation in Hereditary Ataxias (CIRAH) in Holguín, Cuba (Table 1). The SARA was used to clinically assess characteristics and severity of the ataxia [26]. SARA assessment was performed by an independent neurologist blinded to the outcomes of the speech and swallowing assessment and to underlying genotypic status (SCA2 mutation carrier *versus* control; CAG repeat expansion number). According to the common convention [27], participants were classified as pre-ataxic if scored <3 and ataxic if they scored ≥ 3 on SARA (Table 1). Ethical approval was given by the Ethics Committee of CIRAH in Holguín and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

### *Speech Assessment*

Speech and voice samples were recorded using a laptop PC coupled with an external sound card (QUAD-CAPTURE USB 2.0 Audio Interface, Roland Corporation, Shizuoka, Japan) and an AKG 520C condenser microphone (AKG Acoustics GmbH, Vienna, Austria). Participants were required to complete five speech tasks in one sitting:

(i) an unprepared monologue for 1 minute;
(ii) a paragraph reading task (Spanish translation of the North wind and the Sun);
(iii) an automated task, saying the days of week.
(iv) a sequential motion rate (SMR) task ‘pa-ta’ produced as quickly and as clearly as possible for 10 seconds;

Participants were required to perform tasks (ii)-(iv) twice, with the second attempt analyzed, to mitigate any unfamiliarity effects [28, 29]. Speech samples were analyzed acoustically using purpose built scripts run through PRAAT software [30] and are described elsewhere [28, 31, 32]. All tasks were administered and completed in Spanish.

Speech features extracted from recordings included timing metrics (rate, period, perturbation of diadochokinetic [DDK] period, mean pause length, standard deviation of pause length, percentage

of pause, speech rate), voice quality (harmonics to noise ratio (HNR)) and vocal control (coefficient of variation of fundamental frequency [CoV]). Aggregates of the monologue and sustained vowel tasks were also perceptually evaluated across parameters of pitch, loudness, prosody, voice, articulation, resonance and naturalness and intelligibility. Two trained listeners blinded to group (SCA2 mutation carrier versus control) and ataxia severity (SARA score), using a five-point severity scale (0–4; 0=unremarkable, 1=sub-clinical, 2=mild, 3=moderate, 4=severe) and provided consensus perceptual ratings. Oral motor function was assessed using the Frenchay Dysarthria Assessment-2 (FDA-2) [33]. Raters were blinded to the underlying genotypic status (SCA2 mutation carrier versus control), thus guaranteeing a blinded rating, particularly of the pre-ataxic versus control subjects.

***Swallowing Assessment***

A standardized bedside assessment of swallowing was conducted using the Clinical Assessment of Dysphagia in Neurodegeneration (CADN), which has been validated by both swallowing-related quality of life and videofluoroscopic assessment of swallowing in neurodegenerative disease populations, including degenerative ataxias [34]. Participants were screened for risk of penetration and/or aspiration through swallowing trials of different food textures and fluid consistencies. Quantitative data on feeding related activities and their impact on participants including history of chest infection history, independence during mealtimes, and coughing/choking frequency when drinking was derived from the anamnesis component of the CADN. Swallowing-related quality of life was measured using the Eating Assessment Tool (EAT-10), a brief, valid and reliable self-administered questionnaire assessing symptom-specific outcomes of dysphagia and its impact on quality of life [35].

***Statistical Analysis***

SPSS was used for all statistical analyses (IBM SPSS Version 25.0). Parametric comparisons were made on normally distributed data. Where acoustic samples did not present with gaussian distribution, data were Log natural transformed. One-way ANOVA was used to examine between group comparisons. Where significant differences were observed, post hoc pairwise comparisons were conducted to determine the direction and size of those differences. All data derived from the FDA-2, perceptual speech ratings, CADN and EAT-10 were analyzed using non-parametric tests (Kruskal Wallis and Mann-Whitney). Significance was adjusted using the Bonferroni method for perceptual ratings ($p \leq 0.008;(0.05/6)$), acoustic outcomes ($p \leq 0.006;(0.05/9)$) and correlations ($p \leq 0.008;(0.05/6)$). For all other measures, an alpha value was set to 0.05. Data are expressed as the mean ± SD unless otherwise stated.

### *Data Availability*

Anonymized data can be made available by request to the corresponding author, Assoc. Prof Adam P Vogel (vogela@unimelb.edu.au).

## RESULTS:

### ORAL MOTOR FUNCTION IN SCA2

Significant group differences were observed on FDA-2 sub-scales for reflex ($H(2)=10.13$, $p=0.006$) and tongue ($H(2)=8.35$, $p=0.015$) and FDA-2 total score ($H(2)=10.89$, $p=0.004$) (Figure 1). Pre-ataxic SCA2 individuals rated higher on FDA-2 total score ($Z=-2.71$, $p=0.007$) and FDA-2 reflexes ($Z=-3.15$, $p=0.002$) compared to healthy controls. Following adjustment for multiple comparisons, no differences were found on lip and tongue FDA-2 sub-scales in pre-ataxic SCA2 individuals. Ataxic SCA2 individuals were rated higher on FDA-2 tongue sub-scales ($Z=-2.74$, $p=0.006$) compared to healthy controls. Following adjustment for multiple comparisons no differences on lips and reflex FDA-2 sub-scales in ataxic SCA2 individuals when compared to healthy controls.

### SWALLOWING DEFICITS IN SCA2

Significant between group differences were found on all measures of the CADN; anamnesis ($H(2)=11.03$, $p=0.004$), consumption ($H(2)=9.01$, $p=0.011$) and total score ($H(2)=14.15$, $p=0.001$) (Figure 2).

**Pre-ataxic SCA2 individuals.** Higher scores on anamnesis ($Z=-3.52$, $p<0.001$), consumption ($Z=-3.04$, $p=0.002$) and total score ($Z=-3.98$, $p<0.001$) were observed in pre-ataxic SCA2 individuals compared to healthy controls. Nine out of sixteen (56.3%) pre-ataxic SCA2 individuals presented with moderate signs of dysphagia in anamnesis (CADN anamnesis) in comparison to 2/15 (13.3%) of healthy controls. A range of functional deficits were observed across pre-ataxic individuals with evidence of coughing/choking when eating (once a month: 2/16, once a week: 3/16 or once a day: 2/16) and on liquids (once a month: 4/16, once a week: 2/16 or once a day: 1/16). Two SCA2 individuals reported chest infections in the past 12 months. While all pre-ataxic SCA2 individuals were able to eat independently during mealtimes and when drinking (subclinical:1/16), 43.7% presented with difficulty managing saliva (once a month: 2/16, once a week: 3/16 or once a day: 2/16). Some modified their diet to improve swallowing (mild: 3/16). Two out of 15 (13.3%) pre-ataxic SCA2 individuals presented with moderate signs of dysphagia as evaluated by consumption (CADN consumption) with 6/15 rated with subclinical functional deficits in swallowing solids. The overall CADN score indicates that 9/16 (56.3%) pre-ataxic SCA2 individuals have moderate

signs of dysphagia with aspiration risk in contrast to 2/16 (12.5%) healthy controls. No significant group were found between pre-ataxic individuals and healthy controls on measures of swallowing related quality of life (EAT-10).

**Early-stage ataxic SCA2 individuals.** Ataxic SCA2 individuals displayed higher scores on anamnesis (Z=-2.26, $p$=0.02), consumption (Z=-2.25, $p$=0.02) and the CADN total score (Z=-2.26, $p$=0.02) when compared to healthy controls. Five out of fourteen (35.7%) presented with moderate-to-profound signs of dysphagia in anamnesis (CADN anamnesis) in comparison to 2/15 (13.3%) of healthy controls. Evidence of coughing/choking when eating (once a month: 1/14, once a week: 1/14, each meal: 3/14) and on liquids (once a month: 4/16, once a week: 1/14, once a day: 1/14) were observed. Deficits in saliva management were reported (once a month: 2/14, once a week: 2/14, more than once a day: 2/14) in conjunction with dietary modifications to assist swallowing (mild:3/14). Only one out of fourteen (7.1 %) ataxic SCA2 individuals presented with moderate signs of dysphagia with sub-clinical to mild functional deficits in swallowing solids (CADN consumption; sub-clinical:3/14, mild:1/14). Overall, 1/14 (7.1%) and 4/14 (28.6%) ataxic SCA2 individuals had moderate or **s**evere/profound signs of dysphagia with high aspiration risk respectively in contrast to 2/16 (12.5%) and 0/16 healthy controls. There was no difference in swallowing related quality of life, as measured by the EAT-10, between ataxic individuals and healthy controls.

***Relationship with disease severity.*** The relationship between swallowing impairment items (CADN) and SCA2 ataxia severity were examined. No significant relationship was established between disease severity or length of CAG expansion and aspiration/consumption measures of swallowing impairment, indicating that dysphagia deficits occur and progress independently from overall ataxia deficits in SCA2.

## SPEECH DEFICITS IN SCA2

***Pre-ataxic SCA2 individuals*.** Blinded listener ratings of naturalness ($\chi^2(2)=9.207$, $p$=0.01), pitch (monopitch; $\chi^2(2)=11.607$, $p$=0.003), loudness (monoloudness; $\chi^2(2)=7.243$, $p$=0.027), prosody (speech rate; $\chi^2(2)=6.482$, $p$=0.039 and prolonged intervals; $\chi^2(2)=9.481$, $p$=0.009) and articulation (imprecise consonants $\chi^2(2)=7.31$, $p$=0.026) differed between groups (Figure 3). Post hoc comparisons revealed significant differences between pre-ataxic and ataxic SCA2 groups on measures of naturalness ($U$=-2.277, $p$<.05), monoloudness ($U$=-2.316, $p$<0.05) and prolonged intervals ($U$=-2.564, $p$=0.026). These differences disappeared if adjusting significance levels to cater for multiple comparisons. No differences were observed between healthy controls and pre-

ataxic groups. Two of nine acoustic measures differed between groups; reduced speech agility (slower in diadochokinetic rate $p$=0.004; increased diadochokinetic period $p$=0.025) was noted in pre-ataxic SCA2 individuals when compared to healthy controls (Figure 4a-d).

***Early-stage ataxic SCA2 individuals.*** Ataxic SCA2 individuals received higher ratings of monopitch (Z=-3.125; p=0.002), produced speech at a slower rate (Z=-2.240; p=0.043) and had more imprecise consonants (Z=-2.659; p=0.021) compared to healthy controls. Compared to both healthy controls and pre-ataxic groups, ataxic SCA2 individuals displayed abnormal naturalness (vs. healthy controls; Z=-2.709; p=0.014; vs. pre-ataxic Z=-2.277; p=0.043), and higher ratings of monoloudness (vs. healthy controls; Z=-2.114; p=0.016, vs. pre-ataxic Z=-2.316; p=0.048) and prolonged intervals (vs. healthy controls; Z=-2.056; p=0.011, vs. pre-ataxic Z=-2.564; p=0.045) (Figure 3). Four of nine acoustic measures differed between groups; reading speech rate ($F$(2,39)=9.68, $p$<0.001), diadochokinetic rate ($F$(2,43)=14.07, $p$<0.001), diadochokinetic period ($F$(2,43)=12.79, $p$<0.001) and perturbation of diadochokinetic period ($F$(2,43)=6.17, $p$=0.004) (Figure 4a-d). Ataxic SCA2 individuals presented with slower reading speech rate ($p$<0.001) and reduced speech agility (reduction in diadochokinetic rate $p$<0.001; increase in diadochokinetic period ($p$<0.001) and perturbation of diadochokinetic period ($p$=0.004)) compared to healthy controls.

***Relationship with disease severity.*** The relationship between acoustic measures of speech and SCA2 ataxia severity were examined (Figure 4e-h). Diadochokinetic rate (r(44)=-0.46, $p$=0.001) and speech rate (r(42)=-0.49, $p$=0.001) were negatively associated with SCA2 ataxia severity while diadochokinetic period (r(44)=0.48, $p$=0.001) and perturbation of diadochokinetic period (r(44)=0.52, $p$<0.001) were positively associated with SCA2 ataxia severity (Figure 4e-g). This was further explored by assessing the relationship between CAG expansion length and acoustic measures of speech. With the exception of reading speech rate (r(27)=-0.23, $p$=0.25), CAG expansion length inversely correlated diadochokinetic rate (r(30)=-0.52, $p$=0.001) and was displayed strong positive association with diadochokinetic period (r(30)=0.56, $p$=0.001) and perturbation of diadochokinetic period (r(30)=0.62, $p$<0.001)

## RELATIONSHIP BETWEEN TIMING OF ATAXIA ONSET AND SPEECH AND SWALLOWING OUTCOMES

A total of 14 participants were diagnosed with early-stage ataxic SCA2 prior to enrolment in the study. For the remaining 16 pre-ataxic SCA2 participants, predicted time to ataxia onset was calculated as years remaining from subjects' current age (at the time of testing) to the predicted time to ataxia onset according to their CAG expansion size based on calculations specifically from

a Cuban SCA2 population[36]. In pre-ataxic SCA2 subjects, markers of dysphagia and dysarthria were seen at 11.49 years prior predicted time to ataxia onset (Table 2).

The relationship between swallowing impairment (CADN) and speech deficits (acoustic measures of speech agility and rate) and time to ataxia onset were examined. There was no observed relationship between time to ataxia onset and oral motor function or swallowing impairment ($p>0.05$). In contrast, there was a positive correlation with perturbation of DDK period and time to ataxia onset such that the closer to ataxia onset ($r(30)=0.37$, $p=0.04$, Figure 5a), the greater the perturbation of DKK period. Additionally, reading speech rate was also negatively associated with time to ataxia onset ($r(30)=-0.42$, $p=0.03$, Figure 5b). This suggests reading speech rate declines in advance to ataxia onset with severity increasing at and preceding onset.

**DISCUSSION:**

We here demonstrate that dysarthria and dysphagia are common in SCA2 even at early stages of the disease and are in fact present even prior to ataxia onset. During the early-phase ataxic disease stages of SCA2, dysarthria is characterised by short phrases, irregular articulatory breakdowns, reduced speech agility and speech rate, resulting in reduced intelligibility. Timing deficits observed in early-stages of SCA2 resemble those observed in related ataxia disorders such as Friedreich ataxia [16, 32, 37], POLG associated ataxia (POLG-A) [38] and autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) [39].

Pre-ataxic SCA2 present with a subtler speech phenotype characterized by an absence of overt dysarthria (SARA speech disturbance: 100% of individuals rated as ‘normal’), but demonstrated distinct changes in speech timing with reduced rate and consistency of production during syllable repetition tasks. These timing specific deficits (in the absence of voice related impairment) highlight early changes in motor function that precede ataxia symptoms. These early deficits likely reflect an early cerebellar dysfunction, as cerebellar pathways are thought to coordinate timing of motor speech [17, 32, 40]. Deficits are then magnified with manifestation of ataxia disease, i.e. in early-stage SCA2, indicating sensitivity of these speech markers to disease progression and/or change over time.

This notion is further supported by the observation that syllabic rate, average time between vocalizations and variability of syllabic periods correlated with ataxia severity (as measured by SARA). The changes observed on the speech agility tasks manifest as slow and inconsistent syllable productions resulting from increases in average time between vocalizations and increased

variability of the length of each syllabic period, detectable even at the pre-ataxic stage. This highlights the utility of speech agility tasks in which the motor system is challenged through fast repetitive production of unfamiliar sequential movements not typically part of the repertoire of everyday speech. This notion adds further support for our earlier concept, that it is in particular motor challenge tasks which allow to uncover subtle motor deficits in pre-ataxic SCA subjects[41].

In contrast to previous reports demonstrating changes in voice quality in mixed SCA cohorts [17, 40], this study did not detect deficits in perceptual or acoustic voice quality or pitch control measures in either pre-ataxic or ataxic SCA2 patients. This is very likely due to the inclusion of early stages SCA2 disease in this study where individuals had a mean duration of disease of 3.8 years (range = 0-10 years) post clinical diagnosis, and mean SARA score of 6.14 (SARA range = 3-9). Literature has shown that voice quality decline in later stages of SCAs whereby manifestations are present in individuals with a mean disease duration of 15 years [17].

Dysphagia is a common and potentially life-threatening sequelae of disease progression in hereditary ataxias however beyond frequent throat clearing[24] it has not yet commonly been recognised as a frequent *pre*-ataxic feature in SCAs. Here we show that more than half of pre-ataxic SCA2 individuals (56.25%) already presented with moderate swallowing impairment, while 36.5% of ataxic SCA2 individuals had signs of moderate-severe dysphagia. This finding supports previous studies which demonstrate that pharyngeal phase deficits such as penetration and/or aspiration are present in SCAs [20, 21], and highlights that – at least in SCA2 - these deficits might arise before manifest ataxia onset. Despite this occurrence, no significant relationship was established with ataxia severity (as measured by SARA scores) also in ataxic SCA2 subjects. These data differ to other investigations of dysphagia in ataxia [38], with CADN scores typically varying in line with disease severity [34]. These results indicate that that dysphagia is independent to or discrete to overall ataxia dysfunction in SCA2 and reflects at least partially a distinct deterioration process within this multisystemic progressive disease (e.g. due to early brainstem dysfunction in SCA2 [27]).

This study outlines the potential of acoustic analysis of speech, use of speech agility tasks and subjective swallowing measures as quantifiable markers of neurological functioning and as salient markers of disease progression in early-stage SCA2, including stratification of the pre-ataxia phase. In relation to acoustic analysis, the speech protocol described here are known to be stable, reliable and sensitive to change [28]. This has been shown in Huntington's Disease where measures of speech timing were proposed as strong candidate markers for discrimination of prodromal and early stage disease and for tracking disease progression [42]. The reliability and sensitivity of clinical swallowing measures as quantifiable markers of neurological functioning, however, still require further

investigation. The CADN score used here has been validated using videofluroscopic swallowing studies in neurodegenerative disease populations, including degenerative ataxias, with high sensitivity and specificity [34, 43]. Nevertheless, instrumental examination alongside clinical bedside assessments would add deeper understanding of the underlying swallowing deficits.

Whilst our study expands and extends previous characterization work, there are no known treatments to improve speech or swallowing in hereditary ataxias [44, 45] aside from a small case series demonstrating efficacy of intensive biofeedback driven speech treatment [46]. Further research is required to establish sensitivity of speech and swallowing markers in detecting treatment efficacy and disease progression. SARA scores indicate that symptomatic SCA2 individuals were in the early stage of the disease. Longitudinal studies tracking disease progression, with a wider CAG repeat range and cross-correlated with structural and functional brain imaging studies, may assist in validating sensitivity of such markers whilst providing additional information on individual disease progression profiles paving the way towards precision medicine of SCAs.

**TABLE 1. Participant Characteristics**

| | Healthy controls | Pre-ataxic SCA2 | Ataxic SCA2 | *P* |
|---|---|---|---|---|
| **n** | 16 | 16 | 14 | |
| **Sex (n)** | 7M,9F | 5M,11F | 7M,7F | 0.57[a] |
| **Age (years)** | 38.38 ± 10.46 | 39.00 ± 8.86 | 37.79 ± 10.62 | 0.94 |
| *Range* | 18-59 | 18-52 | 18-59 | |
| **Age at ataxia onset (years)** | - | - | 34.00 ± 8.96 | |
| *Range* | - | - | 17-45 | |
| **Ataxia severity (SARA)** | 0.68 ± 0.60 | 0.59 ± 0.69 | 6.14 ± 2.18 | **<0.001[b]** |
| *Range* | 0-2 | 0-2 | 3-9 | |
| **FDA-2** | 18.88 ± 5.62 | 24.81 ± 5.55[c] | 26.62 ± 7.61[d] | **0.004** |
| *Reflex sub-score* | 3.44 ± 0.89 | 5.13 ± 1.89[c] | 4.71 ± 2.05 | **0.006** |
| *Lips sub-score* | 5.62 ± 1.54 | 5.81 ± 1.28 | 6.54 ± 1.76 | 0.10 |
| *Tongue sub-score* | 9.75 ± 4.49 | 13.88 ± 5.16 | 15.23 ± 5.02[d] | **0.02** |

[a]Significant differences were evaluated by Chi squared analysis; [b]Kruskal Wallis H Test used; [c]$p<0.05$ Control vs Pre-ataxic SCA2; [d]$p<0.05$ Control vs ataxic SCA2; All data are represented as mean ± SD. SARA=Scale for the Assessment and Rating of Ataxia; FDA-2=Frenchay Dysarthria Assessment (FDA)-2.

**TABLE 2. Pre-ataxic and ataxic SCA2 demographic information.**

| Ppt | Group | Age (years) | CAG repeats per allele | Predicted age of ataxia onset* (years) | Predicted years to ataxia onset (years) |
|---|---|---|---|---|---|
| **1** | Pre-ataxic | 39 | 22/38 | 43 | -4.3 |
| **2** | Pre-ataxic | 36 | 22/39 | 36 | -0.1 |
| **3** | Pre-ataxic | 46 | 21/35 | 61 | -15.0 |
| **4** | Pre-ataxic | 18 | 22/41 | 36 | -18.0 |
| **5** | Pre-ataxic | 39 | 22/35 | 61 | -22.0 |
| **6** | Pre-ataxic | 26 | 22/36 | 54 | -28.0 |
| **7** | Pre-ataxic | 47 | 29/37 | 49 | -1.5 |
| **8** | Pre-ataxic | 30 | 22/41 | 36 | -6.3 |
| **9** | Pre-ataxic | 33 | 22/37 | 49 | -16.0 |
| **10** | Pre-ataxic | 38 | 22/34 | 69 | -31.0 |
| **11** | Pre-ataxic | 48 | 22/34 | 69 | -21.0 |
| **12** | Pre-ataxic | 42 | 22/35 | 61 | -19.0 |
| **13** | Pre-ataxic | 46 | 22/38 | 43 | 2.7 |
| **14** | Pre-ataxic | 41 | 24/39 | 36 | 4.9 |
| **15** | Pre-ataxic | 43 | 22/35 | 61 | -18.0 |
| **16** | Pre-ataxic | 39 | 22/38 | 43 | 8.7 |
| **17** | Ataxic | 52 | 22/37 | - | - |
| **18** | Ataxic | 45 | 23/37 | - | - |
| **19** | Ataxic | 47 | 22/36 | - | - |
| **20** | Ataxic | 45 | 22/39 | - | - |
| **21** | Ataxic | 49 | 34/39 | - | - |
| **22** | Ataxic | 48 | 22/38 | - | - |
| **23** | Ataxic | 25 | 22/42 | - | - |
| **24** | Ataxic | 40 | 22/37 | - | - |
| **25** | Ataxic | 23 | 21/42 | - | - |
| **26** | Ataxic | 36 | 22/36 | - | - |
| **27** | Ataxic | 18 | 22/44 | - | - |
| **28** | Ataxic | 31 | 22/37 | - | - |
| **29** | Ataxic | 36 | 22/39 | - | - |
| **30** | Ataxic | 34 | 22/41 | - | - |
| | | | **Mean** | **50.44** | **-11.49** |
| | | | **SD** | **11.98** | **12.15** |

*Predicted age of clinical onset calculated as previously described [36]

## APPENDIX:

## APPENDIX 1.

Using this item on the INAS, we have now examined the relationship between slowed saccades and swallowing function (CADN) in SCA2 individuals. Here we show that 62.5% and 43.8 % of pre-ataxic SCA2 individuals already present with dysphagia and slowed saccades, respectively (Table 2). These two dysfunctions, appear to evolve partly distinctively at the pre-ataxic stage, demonstrating considerable inter-individual variability in the evolution of brainstem dysfunctions during the pre-ataxic stage of SCA2.

*Table 1: Prevalence of slowed saccades and dysphagia in pre-ataxic and early ataxic SCA2.*

| | | **Pre-ataxic SCA2** | | **Ataxic SCA2** | |
|---|---|---|---|---|---|
| | | **Not Present** | **Present** | **Not Present** | **Present** |
| **Slowed Saccades** | n (%) | 10 (62.5) | 6 (37.5) | 6 (42.9) | 8 (57.1) |
| **Dysphagia** | n (%) | 7 (43.8) | 9 (56.3) | 9 (64.3) | 5 (35.7) |

## APPENDIX 2. Authors

| **Name** | **Location** | **Role** | **Contribution** |
|---|---|---|---|
| Adam P. Vogel PhD | Centre for Neuroscience of Speech, The University of Melbourne, Victoria, Australia & Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen, Germany & Center for Neurology, University Hospital Tübingen, Germany & Redenlab, Australia | | Design and conceptualized study; collected data; analyzed the data; drafted the manuscript, supervised students, obtained funding and lead the team. |
| Michelle Magee PhD | Centre for Neuroscience of Speech, The University of Melbourne, Victoria, Australia | | analyzed the data; drafted the manuscript |
| Reidenis Torres Vega MSc | Center for Research and Rehabilitation of Hereditary Ataxias (CIRAH), Holguin, Cuba | | Collected data; revised the manuscript. |
| Jacqueline Medrano-Montero DSc | Center for Research and Rehabilitation of Hereditary Ataxias (CIRAH), Holguin, Cuba | | Collected data; revised the manuscript. |
| Melissa P Cyngler MSc | Centre for Neuroscience of Speech, The University of Melbourne, Victoria, Australia | | Analysed data; revised the manuscript. |
| Megan Kruse MSc | Centre for Neuroscience of Speech, The University of | | Analysed data; revised the manuscript. |

| | | | |
|---|---|---|---|
| | Melbourne, Victoria, Australia | | |
| Sandra Rojas MSc | Centre for Neuroscience of Speech, The University of Melbourne, Victoria, Australia | | Analysed data; revised the manuscript. |
| Sebastian Contreras Cubillos MSc | University of Santo Tomas, Talca-Chile & Escuela de Fonoaudiologia, Facultad de Salud, Universidad Santo Tomas, Chile; | | Analysed data; revised the manuscript. |
| Tamara Canento MD | Centre for Neuroscience of Speech, The University of Melbourne, Victoria, Australia | | Analysed data; revised the manuscript. |
| Fernanda Maldonado BSc | Centre for Neuroscience of Speech, The University of Melbourne, Victoria, Australia | | Analysed data; revised the manuscript. |
| Yaimee Vazquez-Mojena BSc | Center for Research and Rehabilitation of Hereditary Ataxias (CIRAH), Holguin, Cuba | | Collected data; revised the manuscript. |
| Winfried Ilg PhD | Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen, Germany & Center for Neurology, University Hospital Tübingen, Germany & German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany | | Design and conceptualized study; collected data; revised the manuscript. |
| Roberto Rodríguez-Labrada PhD | Center for Research and Rehabilitation of Hereditary Ataxias (CIRAH), Holguin, Cuba | | Design and conceptualized study; collected data; revised the manuscript. |
| Luis Velázquez-Pérez MD PhD | Center for Research and Rehabilitation of Hereditary Ataxias (CIRAH), Holguin, Cuba | | Design and conceptualized study; collected data; revised the manuscript. |
| Matthis Synofzik MD | Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen, Germany & Center for Neurology, University Hospital Tübingen, Germany & German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany | | Design and conceptualized study; collected data; analyzed the data; revised the manuscript, supervised students, obtained funding and lead the team. |

## FIGURE LEGENDS:

**FIGURE 1. Frenchay dysarthria assessment (FDA)-2 subset score for reflex, lips and tongue and total score in pre-ataxic and ataxic SCA2.** *$P < 0.05$. Values represent Mean ± SD.

**FIGURE 2. Clinical assessment of dysphagia in neurodegeneration (CADN) and Eating assessment Tool (EAT-10) in pre-ataxic and ataxic SCA2.** *$P < 0.05$. Values represent Mean ± SD.

**FIGURE 3. Differential frequencies in perceptual ratings of speech pre-ataxic SCA-2 and ataxic SCA-2.** *$P < 0.05$, **$P < 0.01$. ***After Bonferroni correction, monoloudness remained significant.

**FIGURE 4. Acoustic measures of syllable repetition and speech timing, and their relationship with SCA2 ataxia severity as measured by SARA.** *$P < 0.05$. Values represent Mean ± SD. Black dotted lines represent 95% Confidence Intervals.

**FIGURE 5. Acoustic measures of syllable repetition and speech timing, and their relationship with onset of ataxia.** Grey circles represent pre-ataxic SCA2 individuals while open circles represent ataxic SCA2 individuals. Dotted lines represent 95% Confidence Intervals.

**REFERENCES:**


1. Geschwind DH, Perlman S, Figueroa CP, Treiman LJ, Pulst SM. The prevalence and wide clinical spectrum of the spinocerebellar ataxia type 2 trinucleotide repeat in patients with autosomal dominant cerebellar ataxia. American Journal of Human Genetics 1997;60:842-850.
2. Lorenzetti D, Bohlega S, Zoghbi HY. The expansion of the CAG repeat in ataxin-2 is a frequent cause of autosomal dominant spinocerebellar ataxia. Neurology 1997;49:1009-1013.
3. Pedroso JL, Braga-Neto P, Escorcio-Bezerra ML, et al. Non-motor and Extracerebellar Features in Spinocerebellar Ataxia Type 2. Cerebellum 2017;16:34-39.
4. Rub U, Brunt ER, Petrasch-Parwez E, et al. Degeneration of ingestion-related brainstem nuclei in spinocerebellar ataxia type 2, 3, 6 and 7. Neuropathology and Applied Neurobiology 2006;32:635-649.
5. Yamada M, Sato T, Tsuji S, Takahashi H. CAG repeat disorder models and human neuropathology: similarities and differences. Acta Neuropathologica 2008;115:71-86.
6. Pulst SM, Nechiporuk A, Nechiporuk T, et al. Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. Nature Genetics 1996;14:269-276.
7. Velazquez-Perez LC, Rodriguez-Labrada R, Fernandez-Ruiz J. Spinocerebellar Ataxia Type 2: Clinicogenetic Aspects, Mechanistic Insights, and Management Approaches. Front Neurol 2017;8.
8. Auburger GW. Spinocerebellar ataxia type 2. Handbook of Clinical Neurology 2012;103:423-436.
9. Magana JJ, Velazquez-Perez L, Cisneros B. Spinocerebellar ataxia type 2: clinical presentation, molecular mechanisms, and therapeutic perspectives. Molecular Neurobiology 2013;47:90-104.
10. Schalling E, Hartelius L. Acoustic analysis of speech tasks performed by three individuals with spinocerebellar ataxia. Folia Phoniatrica et Logopaedica 2004;56:367-380.
11. Schalling E, Hartelius L. Speech in spinocerebellar ataxia. Brain and Language 2013;127:317-322.
12. Federighi P, Cevenini G, Dotti MT, et al. Differences in saccade dynamics between spinocerebellar ataxia 2 and late-onset cerebellar ataxias. Brain : a journal of neurology 2011;134:879-891.
13. Rodriguez-Labrada R, Velazquez-Perez L, Auburger G, et al. Spinocerebellar ataxia type 2: Measures of saccade changes improve power for clinical trials. Movement Disorders 2016;31:570-578.
14. Lu CS, Wu Chou YH, Kuo PC, Chang HC, Weng YH. The parkinsonian phenotype of spinocerebellar ataxia type 2. Archives of neurology 2004;61:35-38.
15. Burk K, Globas C, Bosch S, et al. Cognitive deficits in spinocerebellar ataxia 2. Brain : a journal of neurology 1999;122 ( Pt 4):769-777.
16. Rosen KM, Folker JE, Vogel AP, Corben LA, Murdoch BE, Delatycki MB. Longitudinal change in dysarthria associated with Friedreich ataxia: a potential clinical endpoint. Journal of Neurology 2012;259:2471-2477.
17. Schalling E, Hammarberg B, Hartelius L. Perceptual and acoustic analysis of speech in individuals with spinocerebellar ataxia (SCA). Logopedics Phoniatrics Vocology 2007;32:31-46.
18. Brendel B, Synofzik M, Ackermann H, et al. Comparing speech characteristics in spinocerebellar ataxias type 3 and type 6 with Friedreich ataxia. J Neurol 2015;262:21-26.
19. Barreto Sdos S, Nagaoka JM, Martins FC, Ortiz KZ. Spinocerebellar ataxia: perceptual and acoustic analysis of speech in three cases. Pró-Fono Revista de Atualização Científica 2009;21:167-170.
20. Vogel AP, Fendel L, Paige Brubacher K, Chan V, Maule R. Dysphagia in spinocerebellar ataxia and multiple system atrophy-cerebellar. Speech, Language and Hearing 2015;18:39-43.
21. da Silva Abdulmassih EM, Ghizoni Teive HA, Santos RS. The evaluation of swallowing in patients with spinocerebellar ataxia and oropharyngeal dysphagia: A comparison study of

videofluoroscopic and sonar doppler. International archives of otorhinolaryngology 2013;17:66-73.
22. Matilla-Duenas A. The ever expanding spinocerebellar ataxias. Editorial. Cerebellum 2012;11:821-827.
23. Montes-Brown J, Machado A, Estevez M, Carricarte C, Velazquez-Perez L. Autonomic dysfunction in presymptomatic spinocerebellar ataxia type-2. Acta Neurologica Scandinavica 2012;125:24-29.
24. Velazquez-Perez L, Rodriguez-Labrada R, Cruz-Rivas EM, et al. Comprehensive study of early features in spinocerebellar ataxia 2: delineating the prodromal stage of the disease. Cerebellum 2014;13:568-579.
25. Velazquez-Perez L, Rodriguez-Labrada R, Canales-Ochoa N, et al. Progression of early features of spinocerebellar ataxia type 2 in individuals at risk: a longitudinal study. Lancet Neurology 2014;13:482-489.
26. Schmitz-Hubsch T, du Montcel ST, Baliko L, et al. Scale for the assessment and rating of ataxia - Development of a new clinical scale. Neurology 2006;66:1717-1720.
27. Jacobi H, Reetz K, du Montcel ST, et al. Biological and clinical characteristics of individuals at risk for spinocerebellar ataxia types 1, 2, 3, and 6 in the longitudinal RISCA study: analysis of baseline data. Lancet Neurol 2013;12:650-658.
28. Vogel AP, Fletcher J, Snyder PJ, Fredrickson A, Maruff P. Reliability, stability, and sensitivity to change and impairment in acoustic measures of timing and frequency. Journal of Voice 2011;25:137-149.
29. Vogel AP, Maruff P. Monitoring change requires a rethink of assessment practices in voice and speech. Logopedics Phoniatrics Vocology 2014;39:56-61.
30. Boersma P. PRAAT, a system for doing phonetics by computer. Glot International 2001:341-347.
31. Vogel AP, McDermott HJ, Perera T, Jones M, Peppard R, McKay CM. The Feasibility of Using Acoustic Markers of Speech for Optimizing Patient Outcomes during Randomized Amplitude Variation in Deep Brain Stimulation: A Proof of Principle Methods Study. Front Bioeng Biotechnol 2015;3:98.
32. Vogel AP, Wardrop MI, Folker JE, et al. Voice in Friedreich Ataxia. Journal of Voice 2017;31:243 e249-243 e219.
33. Enderby P, Palmer R. FDA-2: Frenchay dysarthria assessment (FDA-2). PRO-ED 2008:Austin, TX.
34. Vogel AP, Rommel N, Sauer C, et al. Clinical assessment of dysphagia in neurodegeneration (CADN): development, validity and reliability of a bedside tool for dysphagia assessment. Journal of Neurology 2017;264:1107-1117.
35. Belafsky PC, Mouadeb DA, Rees CJ, et al. Validity and reliability of the Eating Assessment Tool (EAT-10). Annals of Otology, Rhinology & Laryngology 2008;117:919-924.
36. Almaguer-Mederos LE, Falcón NS, Almira YR, et al. Estimation of the age at onset in spinocerebellar ataxia type 2 Cuban patients by survival analysis. Clinical Genetics 2010;78:169-174.
37. Folker J, Murdoch B, Cahill L, Delatycki M, Corben L, Vogel A. Dysarthria in Friedreich's ataxia: a perceptual analysis. Folia Phoniatrica et Logopaedica 2010;62:97-103.
38. Vogel AP, Rommel N, Oettinger A, et al. Speech and swallowing abnormalities in adults with POLG associated ataxia (POLG-A). Mitochondrion 2017;37:1-7.
39. Vogel AP, Rommel N, Oettinger A, et al. Coordination and timing deficits in speech and swallowing in autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS). Journal of Neurology 2018;265:2060-2070.
40. Sidtis JJ, Ahn JS, Gomez C, Sidtis D. Speech characteristics associated with three genotypes of ataxia. Journal of communication disorders 2011;44:478-492.
41. Ilg W, Fleszar Z, Schatton C, et al. Individual changes in preclinical spinocerebellar ataxia identified via increased motor complexity. Mov Disord 2016;31:1891-1900.

42. Vogel AP, Shirbin C, Churchyard AJ, Stout JC. Speech acoustic markers of early stage and prodromal Huntington's disease: a marker of disease onset? Neuropsychologia 2012;50:3273-3278.
43. Vogel AP, Rommel N, Sauer C, Synofzik M. Clinical assessment of dysphagia in neurodegeneration (CADN): reliability and validity. European Journal of Neurology 2016;23:226.
44. Vogel AP, Folker J, Poole ML. Treatment for speech disorder in Friedreich ataxia and other hereditary ataxia syndromes. Cochrane Database Syst Rev 2014:CD008953.
45. Vogel AP, Keage MJ, Johansson K, Schalling E. Treatment for dysphagia (swallowing difficulties) in hereditary ataxia. Cochrane Database Syst Rev 2015:CD010169.
46. Vogel AP, Stoll LH, Oettinger A, et al. Speech treatment improves dysarthria in multisystemic ataxia: a rater-blinded, controlled pilot-study in ARSACS. J Neurol 2019;266:1260-1266.

**FIGURE 1.**

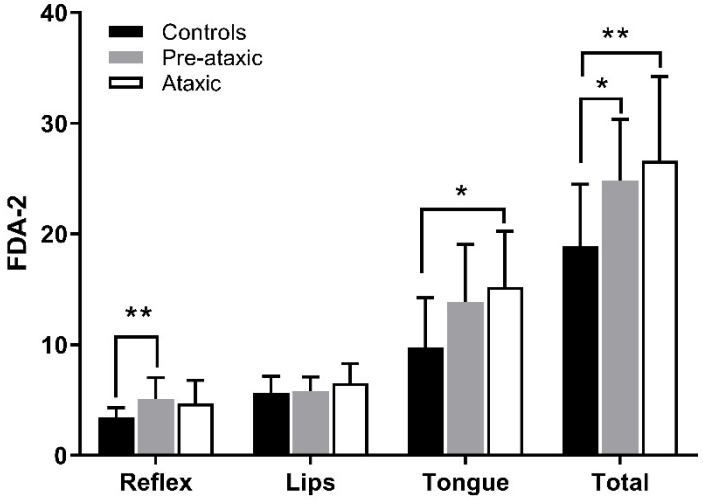

40
30
20
10
0
FDA-2
Controls
Pre-ataxic
Ataxic
**
*
*
**
Reflex
Lips
Tongue
Total

**FIGURE 2.**

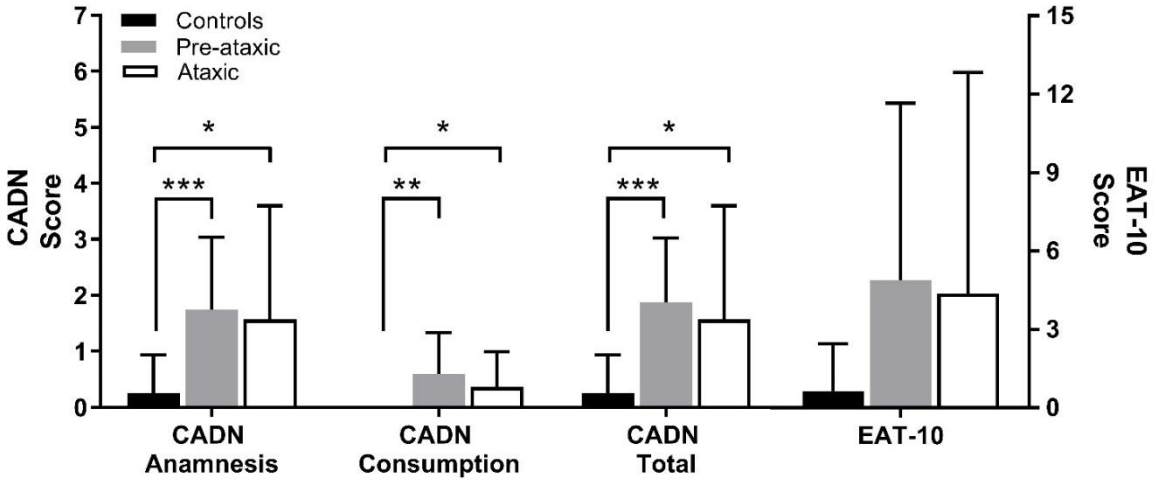

Controls
Pre-ataxic
Ataxic
CADN Score
EAT-10 Score
0
1
2
3
4
5
6
7
0
3
6
9
12
15
*
*
*
***
**
***
CADN Anamnesis
CADN Consumption
CADN Total
EAT-10

**FIGURE 3.**

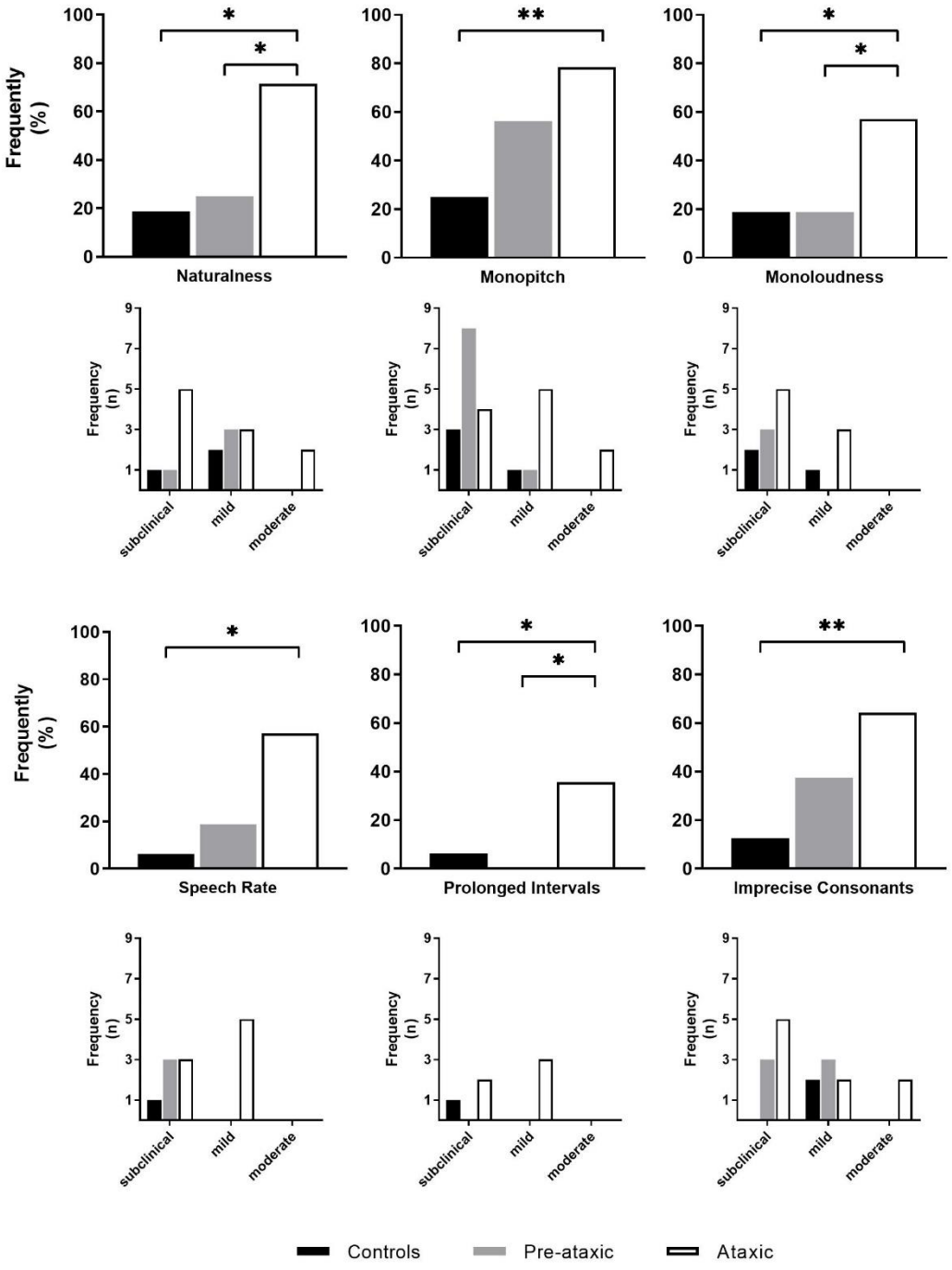

Frequently (%)
Naturalness
Monopitch
Monoloudness
Frequency (n)
subclinical
mild
moderate
Speech Rate
Prolonged Intervals
Imprecise Consonants
Controls
Pre-ataxic
Ataxic

**FIGURE 4.**

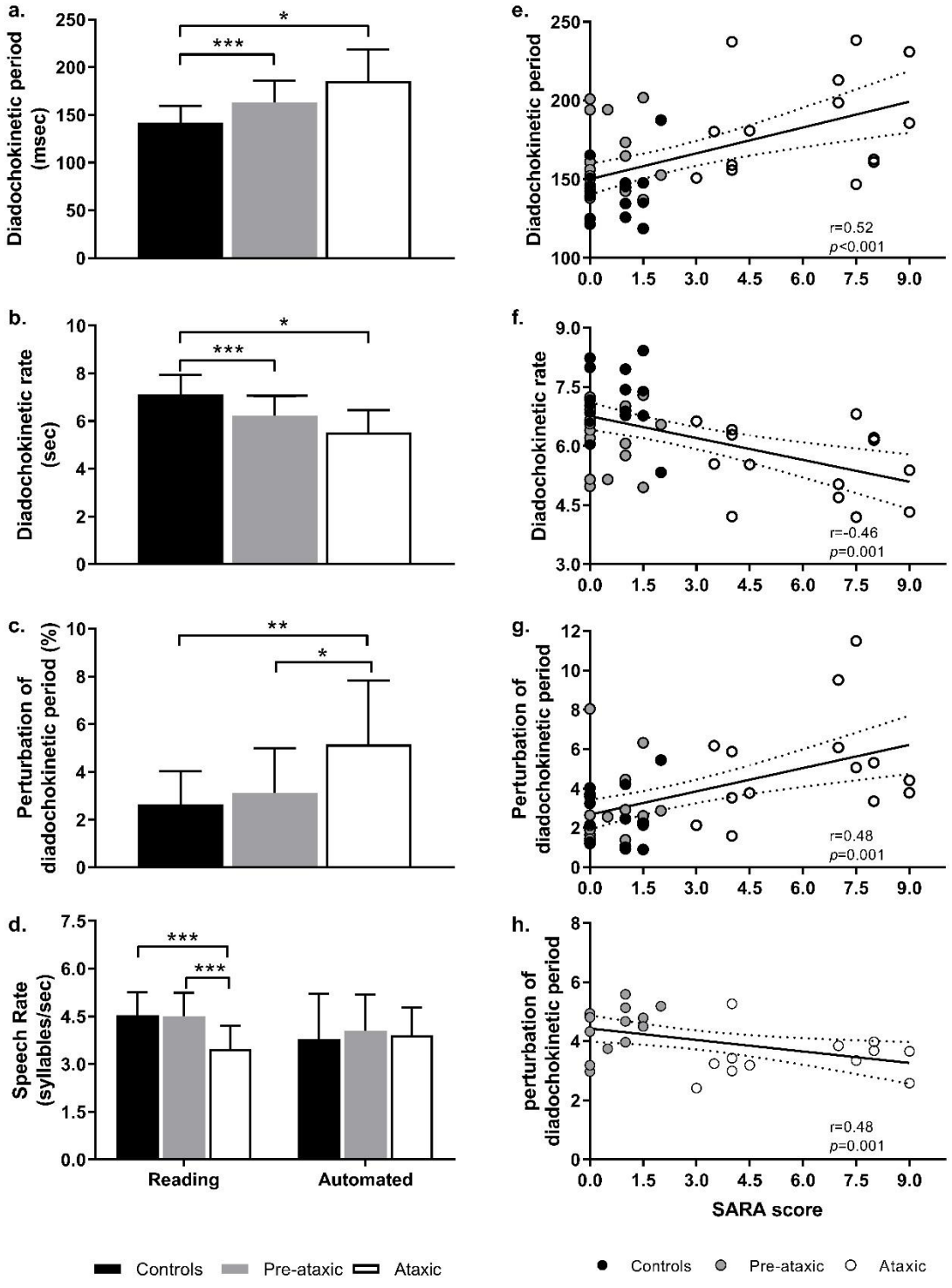
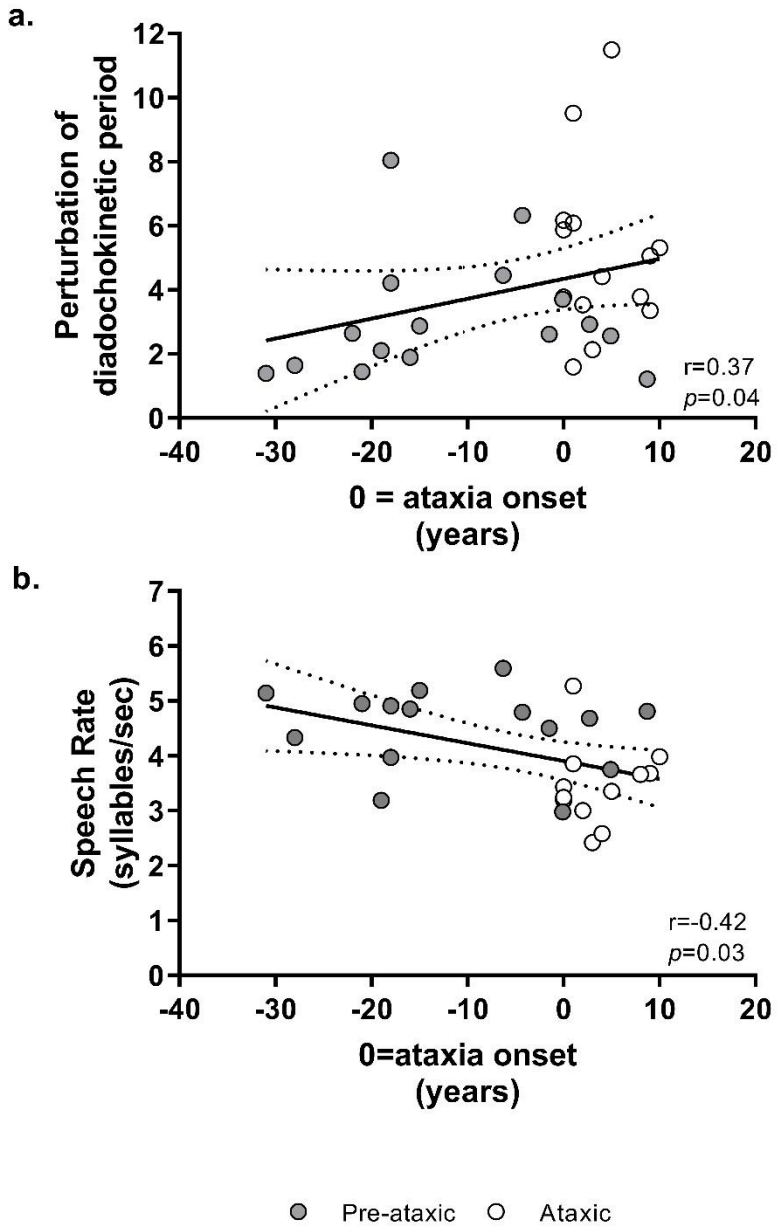

a.
Diadochokinetic period (msec)
250
200
150
100
50
0
***
*
b.
Diadochokinetic rate (sec)
10
8
6
4
2
0
***
*
c.
Perturbation of diadochokinetic period (%)
10
8
6
4
2
0
**
*
d.
Speech Rate (syllables/sec)
7.5
6.0
4.5
3.0
1.5
0.0
***
***
Reading
Automated
Controls
Pre-ataxic
Ataxic
e.
Diadochokinetic period
250
200
150
100
0.0
1.5
3.0
4.5
6.0
7.5
9.0
r=0.52
p<0.001
f.
Diadochokinetic rate
9.0
7.5
6.0
4.5
3.0
r=-0.46
p=0.001
g.
Perturbation of diadochokinetic period
12
10
8
6
4
2
0
r=0.48
p=0.001
h.
perturbation of diadochokinetic period
8
6
4
2
0
r=0.48
p=0.001
SARA score
Controls
Pre-ataxic
Ataxic

**FIGURE 5.**


a.
Perturbation of diadochokinetic period
12
10
8
6
4
2
0
-40
-30
-20
-10
0
10
20
0 = ataxia onset (years)
r=0.37
p=0.04
b.
Speech Rate (syllables/sec)
7
6
5
4
3
2
1
0
-40
-30
-20
-10
0
10
20
0=ataxia onset (years)
r=-0.42
p=0.03
Pre-ataxic
Ataxic

Author/s:
Vogel, AP;Magee, M;Torres-Vega, R;Medrano-Montero, J;Cyngler, MP;Kruse, M;Rojas, S;Cubillos, SC;Canento, T;Maldonado, F;Vazquez-Mojena, Y;Ilg, W;Rodriguez-Labrada, R;Velazquez-Perez, L;Synofzik, M

Title:
Features of speech and swallowing dysfunction in pre-ataxic spinocerebellar ataxia type 2

Date:
2020-07-14

Citation:
Vogel, A. P., Magee, M., Torres-Vega, R., Medrano-Montero, J., Cyngler, M. P., Kruse, M., Rojas, S., Cubillos, S. C., Canento, T., Maldonado, F., Vazquez-Mojena, Y., Ilg, W., Rodriguez-Labrada, R., Velazquez-Perez, L. & Synofzik, M. (2020). Features of speech and swallowing dysfunction in pre-ataxic spinocerebellar ataxia type 2. NEUROLOGY, 95 (2), pp.E194-E205. https://doi.org/10.1212/WNL.0000000000009776.