

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

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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 ataxia²⁶. 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 convention²⁷, 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 software³⁰ 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 \pm 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 severe/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 population³⁶. 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 DDK 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 subjects⁴¹.

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 years¹⁷.

Dysphagia is a common and potentially life-threatening sequelae of disease progression in hereditary ataxias however beyond frequent throat clearing²⁴ 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 ataxia³⁸, with CADN scores typically varying in line with disease severity³⁴. 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 SCA2²⁷).

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 change²⁸. 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 progression⁴². 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 videofluoroscopic 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 treatment⁴⁶. 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	<i>P</i>
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
<i>Range</i>	18-59	18-52	18-59	
Age at ataxia onset (years)	-	-	34.00 ± 8.96	
<i>Range</i>	-	-	17-45	
Ataxia severity (SARA)	0.68 ± 0.60	0.59 ± 0.69	6.14 ± 2.18	<0.001^b
<i>Range</i>	0-2	0-2	3-9	
FDA-2	18.88 ± 5.62	24.81 ± 5.55 ^c	26.62 ± 7.61 ^d	0.004
<i>Reflex sub-score</i>	3.44 ± 0.89	5.13 ± 1.89 ^c	4.71 ± 2.05	0.006
<i>Lips sub-score</i>	5.62 ± 1.54	5.81 ± 1.28	6.54 ± 1.76	0.10
<i>Tongue sub-score</i>	9.75 ± 4.49	13.88 ± 5.16	15.23 ± 5.02 ^d	0.02

^aSignificant differences were evaluated by Chi squared analysis; ^bKruskal 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
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Megan Kruse MSc	Centre for Neuroscience of Speech, The University of		Analysed data; revised the manuscript.

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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 \pm 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 \pm 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 \pm 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.

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FIGURE 1.

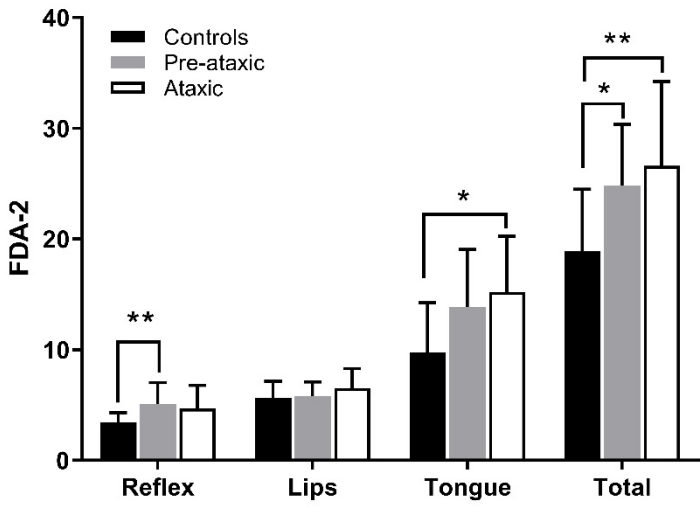


FIGURE 2.

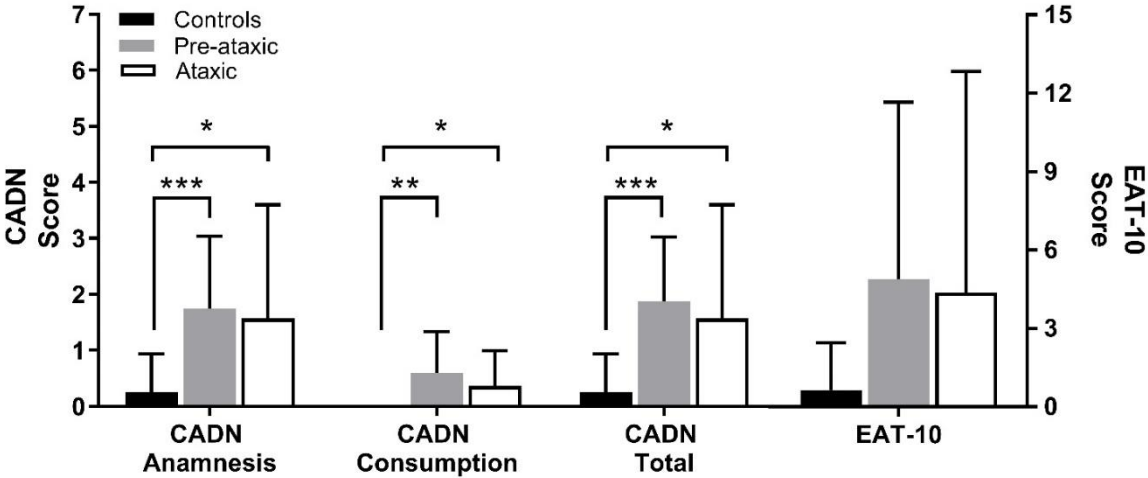


FIGURE 3.

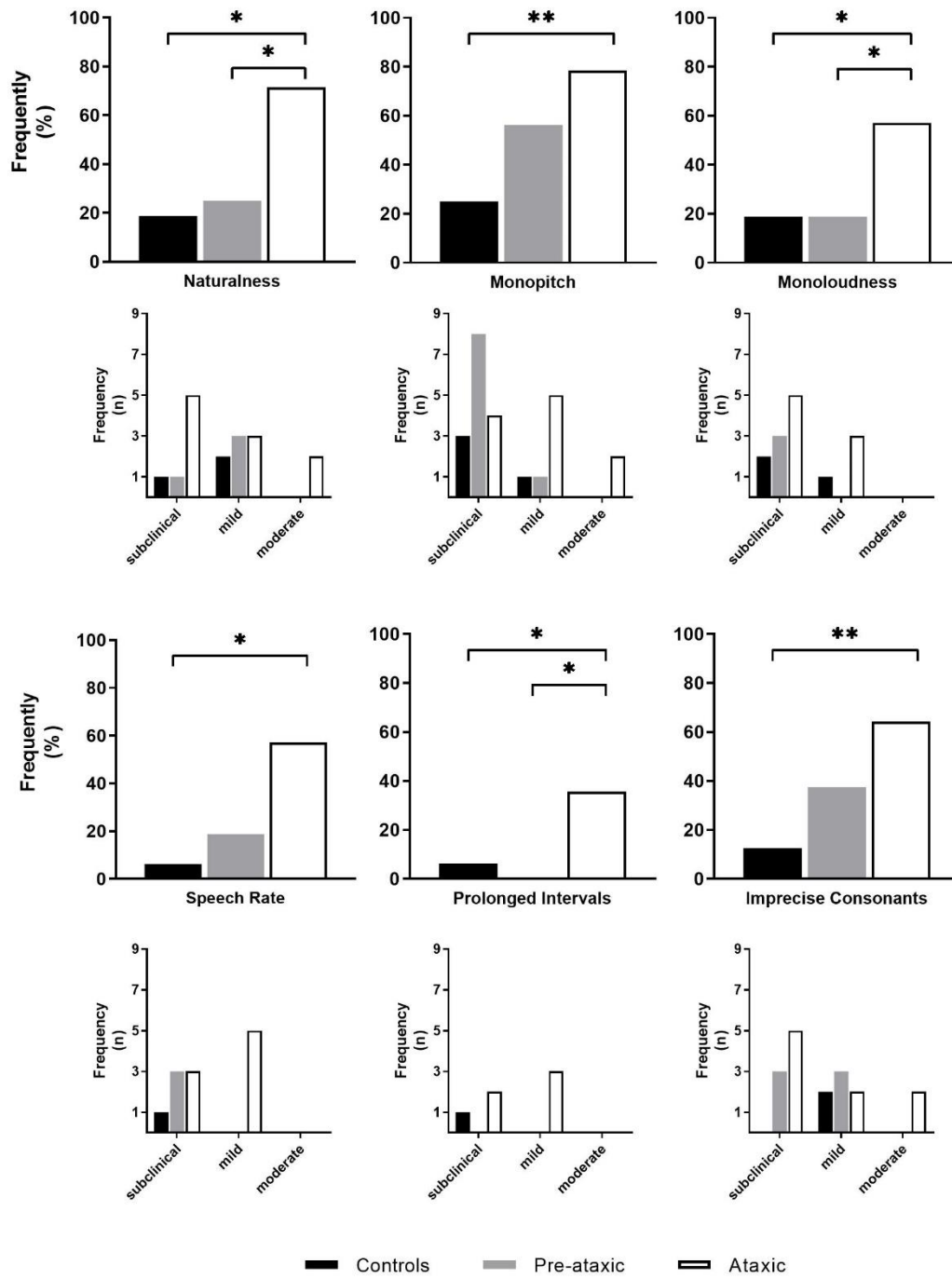


FIGURE 4.

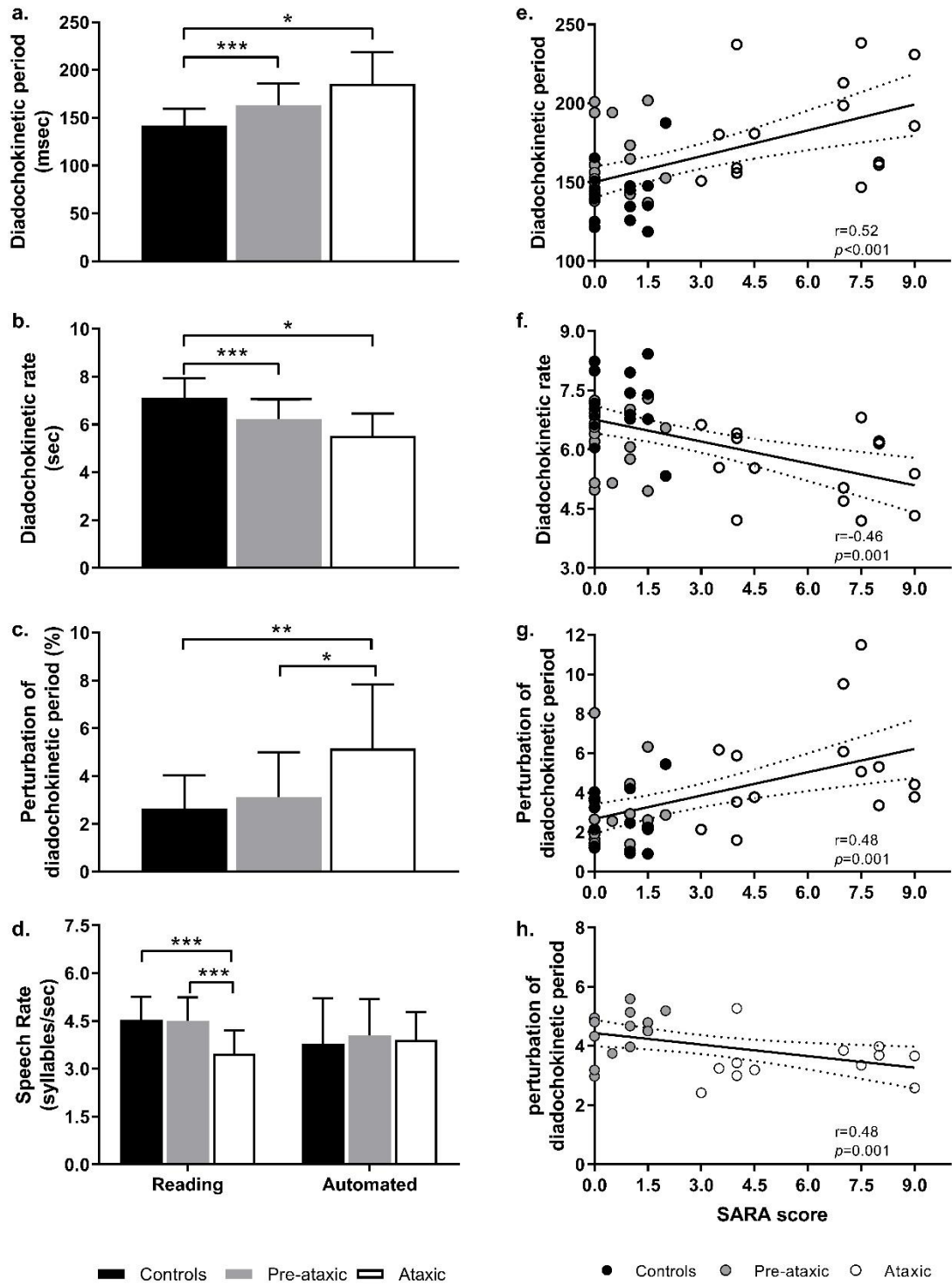
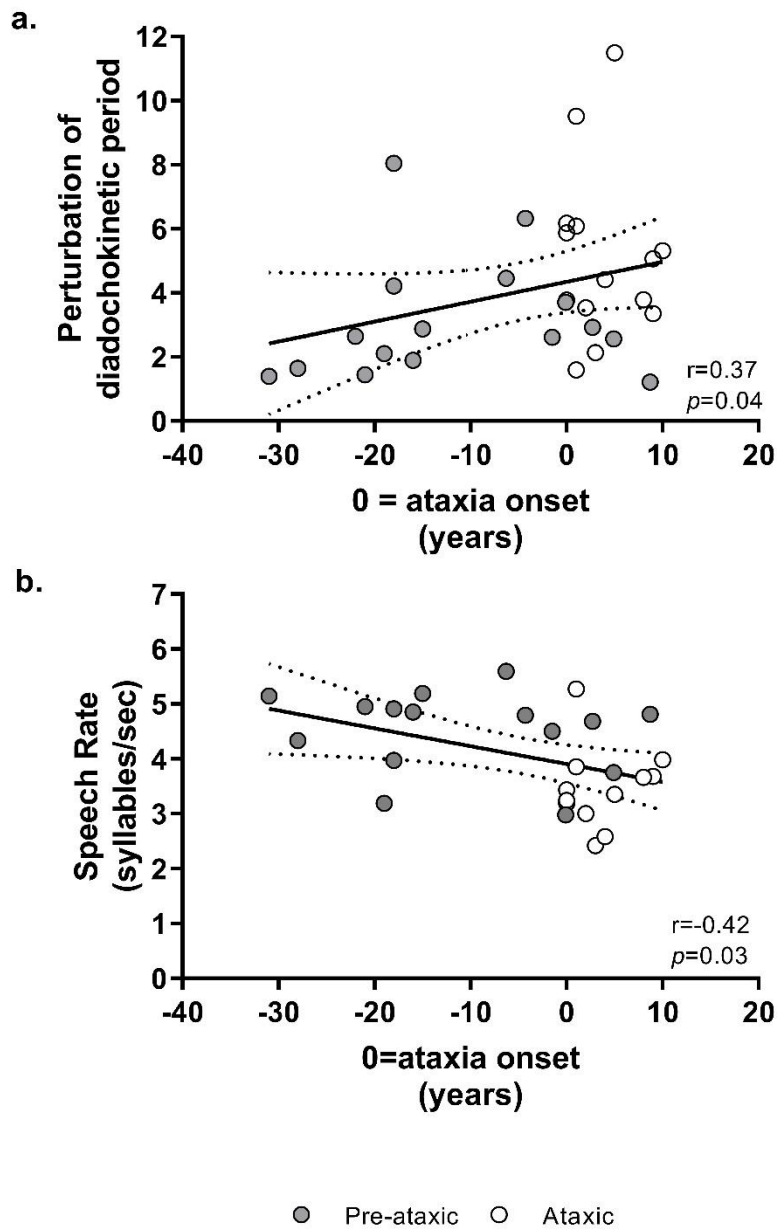


FIGURE 5.





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