

SUCCESSFUL TREATMENT OF AUDITORY PERCEPTUAL DISORDER IN INDIVIDUALS WITH Friedreich ATAXIA

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Abstract—Friedreich ataxia (FRDA) is a neurodegenerative disease affecting motor and sensory systems. This study aimed to investigate the presence and perceptual consequences of auditory neuropathy (AN) in affected individuals and examine the use of personal-FM systems to ameliorate the resulting communication difficulties. Ten individuals with FRDA underwent a battery of auditory function tests and their results were compared with a cohort of matched controls. Friedreich ataxia subjects were then fit with personal FM-listening devices and evaluated over a 6 week period. Basic auditory processing was affected with each FRDA individual showing poorer temporal processing and figure/ground discrimination than their matched control. Speech perception in the presence of background noise was also impaired, with FRDA listeners typically able to access only around 50% of the information available to their normal peers. The use of personal FM-listening devices did however, dramatically improve their ability to hear and communicate in everyday listening situations. © 2010 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: Friedreich ataxia, auditory neuropathy, auditory processing, speech perception.

Friedreich ataxia (FRDA) is a neurodegenerative disease affecting motor and sensory systems due to mutations in the *FXN* gene (Campuzano et al., 1996). Approximately 98% of mutant alleles show an expanded GAA trinucleotide repeat in intron 1 and 2% are point mutations (Cossee et al., 1999).

The auditory consequences of FRDA are common and severe. Affected individuals present with dys-synchrony of neural firing in the central pathways (auditory neuropathy [AN]) despite often displaying normal sound detection (Rance et al., 2008). Electrophysiologic potentials from the cochlear nerve and auditory brainstem are either absent or reduced in amplitude, whereas pre-neural responses (otoacoustic emissions/cochlear microphonics) from the cochlear outer hair cells are typically normal (Rance et al.,

2008). This pattern is consistent with histologic evidence showing preserved cochlear structures in conjunction with specific auditory nerve damage in individuals with FRDA (Spendlin, 1974).

Disruption of neural synchrony can have significant effects on auditory perception in listeners with FRDA. Recent work from our laboratory has revealed impaired temporal resolution (the ability to perceive rapid temporal changes in sounds) and consequent deficits in speech discrimination (which is contingent on the precise representation of brief timing cues) in most cases (Rance et al., 2010). Impairment of speech perception, which is common to all forms of AN, is particularly obvious in the presence of background noise, even at signal-to-noise ratios (SNRs) experienced in everyday listening environments such as offices or school classrooms (Rance et al., 2008).

Amelioration of the functional effects of AN is challenging. Conventional hearing aids amplify sounds but are not designed to clarify temporally distorted signals. Furthermore, they do not significantly improve the SNR of speech in background noise and as such, have been consistently unpopular in trials involving adults with neurodegenerative auditory neuropathy (Rance, 2005). An alternative approach, which is specifically designed to improve listening in noise and has proven beneficial for individuals with peripheral (cochlear) hearing loss, involves the use of FM-listening devices (Hawkins, 1984). These systems transmit speech signals (detected by a lapel-worn microphone) via radio-waves to ear level receivers worn by the listener. Thus, the listener obtains a SNR advantage from the proximity of the speaker's mouth to the transmitter microphone.

Our study aims were to investigate the presence and perceptual consequences of auditory neuropathy in subjects with FRDA and to examine the efficacy of FM-listening systems in this population.

EXPERIMENTAL PROCEDURES

Ten subjects (four females) homozygous for GAA expansion of intron 1 of the *FXN* gene were recruited through the FRDA clinic at the Monash Medical Centre. As each subject was given the FM device at the end of the trial and as we had a limited number of systems, preference was given to school-aged children and adult subjects known to experience communication difficulties in background noise. Age at assessment ranged from 8 to 42 years and age at disease onset ranged from 5 to 20 years. See Table 1 for details. Sound detection was essentially normal in all cases with 4-frequency average hearing level varying from 8.75 to 30 dBHL. Overall disease severity was measured using the Friedreich ataxia rating scale (FARS; Subramony et al., 2005). The FARS is scored out of 167, a higher score indicating a greater level of

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Abbreviations: ABR, auditory brainstem response; AM, amplitude modulation; AN, auditory neuropathy; APHAB, abbreviated profile of hearing aid benefit; FARS, Friedreich ataxia rating scale; FRDA, Friedreich ataxia; SNR, signal-to-noise ratio.

Table 1. FRDA subject details

Subject	Age at assessment (y)	Age at onset (y)	Disease duration (y)	GAA1 (repeat#)	FARS	4 Freq average (dB)	ABR	AM detection (dB)	Masking (dB)
#1	8	5	3	750	62	15.00	Present	−6	25
#2	11	6	5	1298	86	13.75	Present	−6	25
#3	14	10	4	833	73	8.75	Absent	−3	25
#4	17	12	5	818	45	16.25	Present	−9	25
#5	21	6	15	1015	113	30.00	Absent	0	20
#6	30	20	10	700	88	27.5	Absent	−3	25
#7	34	5	29	1099	130.5	25	Absent	0	20
#8	34	13	21	645	121	27.5	Absent	0	20
#9	37	14	23	853	118	16.25	Absent	0	20
#10	42	10	32	706	117.5	18.75	Absent	−3	20

functional disability. Scores ranged from 45 to 130.5 and as such, were fairly representative of our larger FRDA cohort. Findings for each individual are shown in Table 1. Data were also obtained from a group of age, gender and hearing-level matched control subjects. Approval for the study was obtained through the Royal Victorian Eye/Ear Hospital Ethics Committee and all subjects gave written, informed consent prior to inclusion.

Auditory brainstem response (ABR) testing was completed using rarefaction-polarity clicks as per Rance et al. (2008). If the ABR was absent, testing with compression-polarity stimuli was undertaken to confirm the presence of the cochlear microphonic (The CM can be differentiated from the auditory neural response when it changes phase with alteration in stimulus polarity). Each FRDA subject showed evidence of abnormal auditory-neural function. In seven cases, the ABR was absent to stimuli at maximum presentation levels (100 dBnHL) despite normal pre-neural responses. In three subjects, repeatable, but low amplitude ABRs were obtained (Fig. 1).

Two aspects of basic auditory processing, temporal resolution and simultaneous masking, were investigated using psychophysical test techniques as described in Rance et al. (2004). Each

subject was presented with strings of 500 ms stimuli (with 500 ms inter-stimulus periods) and trained to respond when he/she perceived a group of three “target” stimuli inserted randomly into the sequence. Each ear was assessed individually and the stimuli were presented via ER-4 insert phones. Psychometric functions were constructed for each test stimulus and discrimination threshold was the parameter value at which the target could be identified on 70% of occasions. Test order was randomized and repeated measures showed no order effects.

Temporal resolution was assessed using a task which sought the minimum detectable depth for sinusoidal amplitude modulation (AM) at a modulation rate of 150 Hz. The background stimuli were broadband noise bursts and the modulated (target) stimuli were generated by multiplying the noise burst with a dc-shifted sine wave. Depth of modulation (defined as 20 logm) was varied in 3 dB steps from 0 to −30 dB. Presentation levels for both target and background stimuli were randomly varied between 82 dB SPL and 88 dB SPL to reduce the risk that the targets could be identified on the basis of loudness cues.

The masking effect of simultaneous noise was determined by establishing the minimum level of white noise required to obscure a 1 kHz tone at 70 dB SPL. In this experiment, the background stimuli were again 500 ms noise bursts. The targets were noise bursts presented with the pure tone. Spectrum levels of the maskers ranged from 10.5 dB SPL/cycle to 60.5 dB SPL/cycle and the step size was 5 dB.

Each FRDA subject was fitted with a Phonak Inspiro FM-transmitter paired with bilateral iSense ear-level receivers. No gain was required as each of the subjects enjoyed normal or near-normal sound detection. Speech perception testing (consonant-nucleus-consonant [CNC] words) (Peterson and Lehiste, 1962) was then conducted with the subject seated between two loudspeakers. The front loudspeaker presented speech calibrated to reach the subject at 65 dB SPL while the rear speaker provided noise at the same level. Perceptual ability was assessed in both unaided and aided (FM) conditions. For aided testing, the FM-transmitter microphone was suspended 20 cm in front of the “speech” loudspeaker to replicate typical device distance in everyday use. Control subjects were also tested in both unaided and aided conditions.

Day-to-day listening ability was investigated across a 6 week device trial (FRDA subjects only). The children (and their teachers) were encouraged to use the system in school situations where the teacher was the primary speaker. In some cases, the child also wore the FM for noisy extra-curricular activities (watching television, etc.). Adult subjects used the FM in a range of acoustically challenging communication contexts. Duration of device use was not directly measured, but participants typically reported 1–5 h device use per day. Subjects completed a hearing disability questionnaire (abbreviated profile of hearing aid benefit [APHAB]) before FM fitting, after 2 weeks device use, after a

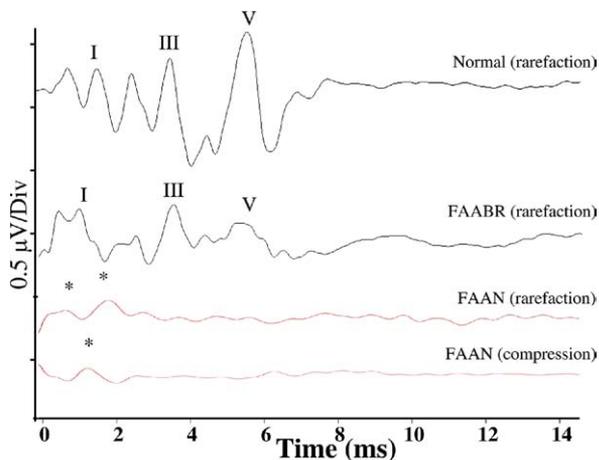


Fig. 1. ABR recordings to acoustic-click stimuli presented at 90 dBnHL. The top tracing shows the combined waveform for the normal cohort (averaged response from 20 ears). The second tracing shows the combined waveform for FRDA ears showing a recordable auditory brainstem response (averaged response from 6 ears). The lower tracings are the combined responses obtained from FRDA ears with no recordable brainstem potentials (14 ears) to rarefaction and compression polarity stimuli. Asterisks denote the positive peaks in the cochlear microphonic potential. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

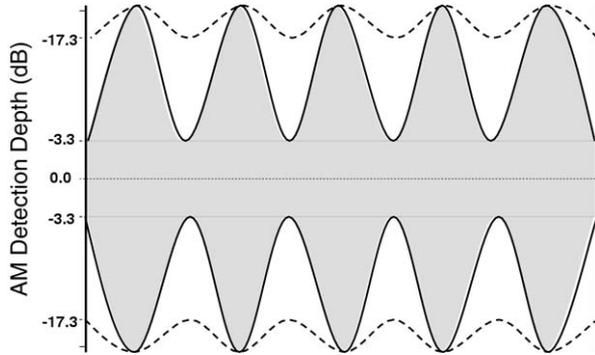


Fig. 2. Diagram showing amplitude modulation of a continuous white noise stimulus. The mean depth required for 150 Hz modulation detection in the FRDA group (-3.3 dB) is shown in grey. The mean depth required by the control group (-17.3 dB) is represented by the dashed line.

further 2 weeks use and finally after 2 weeks of non-use. The APHAB explores four aspects of auditory function: communication difficulty, the effect of background noise, the effect of reverberation and aversiveness to sound. Control subjects completed the questionnaire once.

RESULTS

Detection of sinusoidal amplitude modulation was poorer in FRDA subjects than matched controls. Mean detection threshold for the FRDA group was -3.3 ± 3.6 dB (68.4% of the maximum amplitude) and for the control group was -17.3 ± 2.1 dB (13.6% of maximum) (Fig. 2). Paired T-testing showed a significant difference between matched subjects ($T=13.1$, $P<0.001$). AM detection thresholds for each of the FRDA subjects are shown in Table 1.

The masking effect of simultaneous noise was also greater in FRDA subjects than their matched counterparts. The mean (minimum) level of noise required to render the signal tone inaudible was 23.2 ± 2.7 dB/cycle for the FRDA group and 44.0 ± 3.4 dB/cycle for the controls (Fig. 3). Paired T-testing showed a significant difference between matched subjects ($T=-16.33$, $P<0.001$). Findings for the FRDA individuals are shown in Table 1.

The relationship between these two measures of basic auditory processing (AM detection and simultaneous masking) and a range of patient characteristics was investigated for the FRDA group. Pearson r analyses found

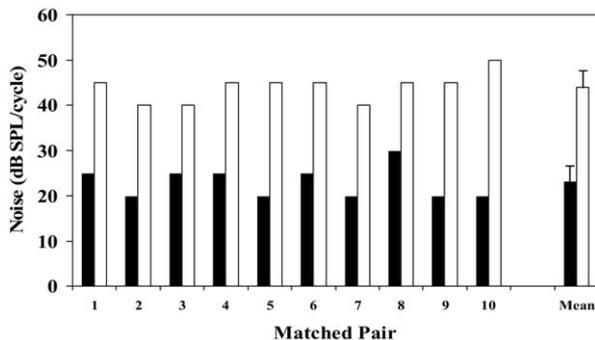


Fig. 3. Minimum noise level required to mask a 1 kHz pure tone for each FRDA subject (filled bar) and their matched control (unfilled bar).

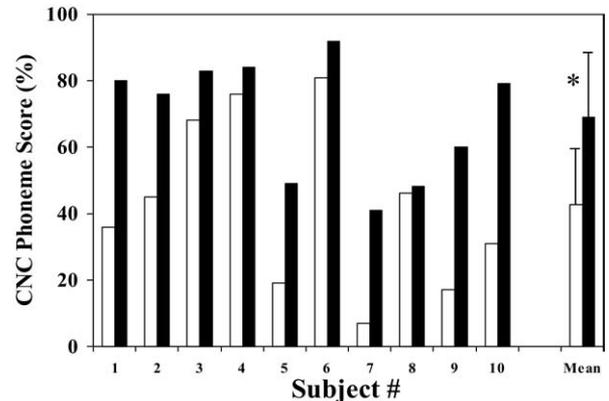


Fig. 4. Open set speech perception score for each FRDA subject obtained in the unaided (unfilled bars) and FM-aided (filled bars) conditions.

significant correlations between both psychophysical tests and age at assessment (AM: $r=0.673$, $P=0.03$; masking: $r=-0.770$, $P=0.009$), disease duration (AM: $r=0.696$, $P=0.02$; masking: $r=-0.900$, $P=0.001$) and FARS score (AM: $r=0.881$, $P=0.01$; masking: $r=-0.898$, $P=0.001$). That is, as subject age, disease duration and overall level of disability increased, AM detection became worse and the masking effect of white noise became more pronounced. No correlation was found between either of the psychophysical tests and age at disease onset or GAA1 repeat size ($P>0.05$).

Speech perception in noise was poorer in the FRDA listeners than controls. Mean phoneme score (the percentage of speech-sounds correctly imitated) for the FRDA group was $42.5 \pm 26.1\%$ and for the control group was $80.1 \pm 1.8\%$ ($T=-4.53$, $P<0.005$). Importantly, perceptual ability was significantly improved in the FRDA listeners when wearing the FM device ($T=-4.87$, $P<0.005$). This benefit is demonstrated in Fig. 4 which shows the unaided and aided speech perception scores for each individual. Group mean score in the aided condition was $69.1 \pm 18.1\%$ and mean aided improvement was $26.5 \pm 17.2\%$.

Prior to the FM trial, the FRDA subjects considered their day-to-day listening and communication to be impaired in a wide range of circumstances. The mean overall APHAB score (representing the proportion of situations in which the individual perceived a difficulty) was $40.2 \pm 11.5\%$. In contrast, the mean APHAB score for the control group was significantly lower: $8.3 \pm 4.5\%$ ($T=8.16$, $P<0.001$).

FM device use produced significant listening and communication improvements for the FRDA cohort. APHAB scores across the four data collection points were; Unaided1: $40.2 \pm 11.5\%$; Aided1: $20.6 \pm 7.5\%$; Aided2: $17.1 \pm 5.2\%$; Unaided2: $38.3 \pm 12.1\%$. Analysis of variance showed a significant group difference ($F_{(3,36)}=15.61$, $P<0.001$). Post hoc analysis found that both aided data points were significantly lower than the unaided ($P<0.05$). As no difference was obtained between the two aided- and two unaided points, the data were collapsed. Fig. 5 shows mean unaided and aided scores across the four listening categories.

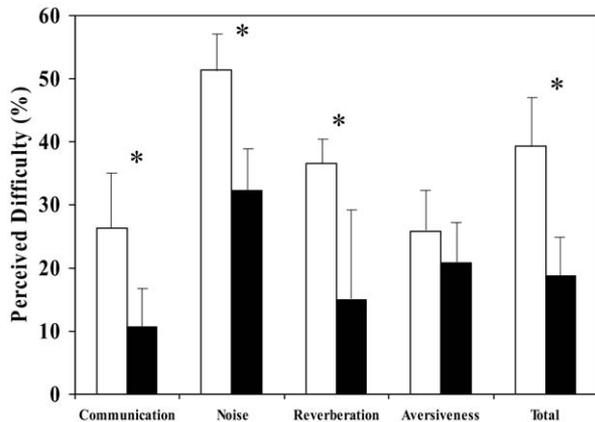


Fig. 5. APHAB hearing disability questionnaire results for unaided (unfilled bars) and aided (filled) conditions. Asterisks represent the metrics in which there was a significant difference between conditions ($P < 0.001$).

DISCUSSION

These data demonstrate the presence of auditory neuropathy and severe disruption of central auditory processing in individuals with FRDA. Each subject suffered an impaired ability to detect rapid signal changes suggesting a temporally distorted representation of auditory events (Zeng et al., 2005). Furthermore, they all showed a reduced ability to extract a tonal signal from within a background masking noise. Similar results have been reported previously for AN due to other forms of neurodegenerative disease (Zeng et al., 2005).

The degree to which auditory processing was affected in individuals with FRDA was highly correlated with overall disease progression (FARS) suggesting that measures of auditory function may prove useful biomarkers, capable of quantifying the natural history of FRDA and assessing the effects of experimental therapies. The fact that we found no relation with measures of genetic severity (age at onset/GAA1 repeat length) further supports the use of auditory psychophysical measures as biomarkers, suggesting they will be better able to monitor the effect of therapeutic interventions than less independent measures. However, further investigation is warranted as the size of the cohort in this study was small.

The major functional consequence of auditory perceptual disorder in listeners with Friedreich ataxia is an impaired ability to understand speech signals in the presence of background noise. In this study the FRDA subjects could only access around half the speech information available to their normal peers. As a result, they all experienced hearing/communication difficulties in even relatively quiet real-world situations.

Personal FM listening devices were successfully fitted to each of the subjects with FRDA in this study. Overall aided performance was not elevated to the level of the controls (reflecting the signal distortion introduced into the auditory system by the neural abnormality), but significant perceptual and communication improvements were achieved in all

cases. Similar outcomes have been reported for subjects with peripheral hearing loss (Hawkins, 1984) and auditory processing disorder (Johnstone et al., 2009), but this is the first data to suggest a viable acoustic management option for listeners with severe temporal processing deficit due to auditory neuropathy. We believe that this has very practical applications to improve quality of life in those with FRDA.

CONCLUSION

Basic auditory processing was affected with each FRDA individual showing poorer temporal processing and figure/ground discrimination than their matched control. Functional hearing, particularly the perception of speech in background noise, was also impaired with FRDA listeners typically able to access only around 50% of the information available to their normal peers. The use of personal FM-listening devices did however, dramatically improve their ability to hear and communicate in everyday listening situations.

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