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Published in:
Clinical Neurophysiology

DOI:
10.1016/j.clinph.2019.10.021

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INTRODUCTION

Friedreich ataxia (FRDA) is the most common recessive ataxia in Caucasians. Over 95% of patients are homozygous for the hyperexpansion of a GAA triplet repeat in the first intron of the frataxin (*FXN*) gene, which represses *FXN* expression via an epigenetic mechanism. Most residual *FXN* expression comes from the chromosome with the shortest repeat (GAA1), whose length has been shown to correlate with age at symptom onset and with disease severity. Clinically, FRDA is dominated by a tabeto-cerebellar ataxic pattern, associated with pyramidal signs and various systemic manifestations. FRDA patients may present subtle signs of proprioceptive loss, such as loss of tendon reflexes and a Romberg sign, before they become frankly symptomatic. However, FRDA patients become overtly ataxic only when cerebellar symptoms appear. Most items in the scales for the assessment of neurological deficits in FRDA (e.g., Scale for the Assessment and Rating of Ataxia (SARA) or the Friedreich Ataxia Rating Scale) are performed under patients' visual control and mainly reflect cerebellar dysfunction rather than afferent proprioceptive ataxia. Neuroimaging studies show progressive thinning of the cervical spinal cord, but to what extent this is due to shrinking of pyramidal tracts or the posterior columns is unclear (Koeppen et al. 2017; Dogan et al. 2019).

Cortico-kinematic coherence (CKC) is the coupling between movement-related proprioceptive inputs and contralateral primary sensorimotor (SM1) cortex activity recorded by magnetoencephalography (MEG) or electroencephalography (Marty et al. 2019). It is an electrophysiological marker of spino-cortical proprioceptive function that has high test-retest reliability (Piitulainen et al. 2018). In a cohort of FRDA patients, we showed that CKC levels were reduced by about 70% and correlated with the size of GAA1 triplet expansion and the age of symptoms onset suggesting that proprioceptive impairment in FRDA was genetically determined and scarcely progressive after symptoms onset (Marty et al. 2019).

Here, we re-tested the same FRDA patients after 1 year to assess whether CKC levels deteriorate over time or tend to remain stable, supporting an early developmental proprioceptive impairment.

METHODS

The methods used in the present study are described in (Marty et al. 2019). CKC was evaluated using whole-scalp-covering MEG (Vectorview & Triux, MEGIN, Helsinki, Finland) in 16 FRDA patients (10 females, one left-handed, mean ± SD age 27 ± 14 years, GAA1 698 ± 203) in two sessions performed at about one-year interval (13.3 ± 4 months). CKC was evaluated during active right forefinger–thumb opposition movements (*Active*, *n* = 15: one patient was too disabled to perform the task) and during passive right forefinger flexion–extensions (*Passive, n* = 16) at about 3 Hz. Forefinger acceleration was monitored with an accelerometer. Movement frequency and regularity were determined in *Active*. Coherence maps at movement frequency (F0) and its first harmonic (F1) were computed at the group-level. Their statistical differences between sessions were assessed with a nonparametric permutation test. Movement frequency and regularity parameters in *Active* as well as SARA scores between the two sessions were compared with a two-tailed paired Student's T-test.

RESULTS (Table 1)

SARA score significantly deteriorated between the two sessions while movement frequency and regularity in *Active* remained stable**.** At the group level, no significant difference was found between CKC levels at contralateral SM1 cortex between the two sessions for both *Active* and *Passive*. Figure 1 illustrates sensor-level coherence spectra in *Active* and the corresponding group-level source reconstructions.

	Session 1	Session 2	*p*
SARA (mean±SD) / 42 **Lower limb items (mean±SD) /** 18 Upper limb items (mean±SD) / 12	21.2± 8.7 11.8± 5.3 5.8± 2.1	22.9± 8.3 12.8± 4.6 5.9± 2.1	**0.0063** **0.016** 0.48
9HPT (seconds, mean±SD)	79± 41	74± 32	0.31

Movement frequency (Hz, mean±SD)	1.87 ± 0.61	1.92 ± 0.63	0.78
Movement regularity (Hz, mean±SD)	0.44± 0.06	0.46± 0.08	0.58
CKC F0 in ***Active***	0.08	0.07	0.40
CKC F1 in ***Active***	0.04	0.05	0.69
CKC F0 in ***Passive***	0.08	0.05	0.08
CKC F1 in ***Passive***	0.05	0.03	0.39

Table 1. Longitudinal evolution of clinical scores, movement characteristics and CKC. SARA =scale for the assessment and rating of ataxia. "/ " separates the clinical score from the maximal rating, higher scores corresponding to worse performance. SARA Lower limb items = gait /8, stance /6 & heel to shin /4. SARA Upper limb items = Finger chase /4, Nose to finger /4 & fast alternating movement /4. SD = standard deviation, 9HPT = nine holes peg test. CKC= corticokinematic coherence. F0 = movement frequency. F1 = first harmonics of movement frequency.

DISCUSSION

This prospective study demonstrates that FRDA patients have stable CKC levels at one-year follow-up, while their SARA score significantly worsens.

Anomalies in dorsal root ganglia (DRGs), dorsal roots and posterior columns of the spinal cord that underlie afferent ataxia are already pronounced early in the course of FRDA and may be, at least in part, developmental. By contrast, cerebellar pathology, mostly consisting in dentate nucleus atrophy, can only be detected after several years of disease progression (Koeppen et al. 2017). However, there also is evidence of active neurodegeneration with an inflammatory component in DRGs (Koeppen et al. 2017), suggesting that proprioceptive loss may progress over time. So, the contribution of proprioceptive loss to the worsening of ataxia in FRDA remains unsettled.

Functionally, reduction in the amplitude of somatosensory evoked potentials (SEPs) and magnetic fields (SEFs) correlates with the size of GAA1 triplet expansion but not with disease duration (Naeije et al. 2019). Still, tactile perception is less impaired in FRDA, limiting the interpretation of these results (Naeije et al. 2019). Similarly, CKC levels are substantially reduced in FRDA patients and correlate with the size of GAA1 triplet expansion but not with disease duration nor SARA score (Marty et al. 2019). In this study, FRDA patients had stable CKC levels at one-year follow-up, while their SARA score significantly

deteriorated. This latter finding therefore corroborates previous SEP, SEF and CKC data supporting early, scarcely progressive proprioceptive defect in FRDA (Marty et al. 2019).

In this study, clinical markers such as the 9HPT, finger movement frequency and regularity during *Active* did not show significant changes at one-year of follow-up. Thus, the SARA score had a higher sensitivity to progression than other clinical measures. However, these additional measures, such as CKC as used in this study, assessed upper limb function whereas the SARA score is largely driven by performance in gait and stance items until late in the course of FRDA. At that stage, upper limb items drive further the SARA score progression, but the overall sensitivity of the scale decreases. Importantly, a significant deterioration of lower limb items of the SARA score was observed at one-year interval, while upper limb items remained stable. In that context, our results could be interpreted either as the consequence of an insufficient sensitivity of the measures used to assess progression, as lack of progression of the measured function or as a too slow deterioration of upper limb proprioceptive function to be detected after only one year. Lower limb CKC studies would have been of great interest in that context but were infeasible due to the FRDA-induced feet deformations, amyotrophy, spasticity and the impossibility for most patients to perform toe or ankle repetitive movements.

In any case, this study provides an objective assessment of upper limb spino-cortical proprioceptive function in FRDA patients over time that is clearly abnormal but fails to show significant worsening over one year. This finding provides additional empirical evidence suggesting limited progressivity of an early established dorsal columns and DRG pathology.

Conflict of interest statement:

None of the authors have potential conflicts of interest to be disclosed.

Acknowledgments:

This study was financially supported by the research grant “Les Voies du Savoir” from the Fonds Erasme (Brussels, Belgium), the Fonds de la Recherche Scientifique (FRS-FNRS,

Brussels, Belgium; research credit: J.0095.16.F), and a research grant from the Friedreich Ataxia Research Alliance (FARA, Drs Massimo Pandolfo). Xavier De Tiège and Gilles Naeije are Postdoctorate Clinical Master Specialist at the Fonds de la Recherche Scientifique (FRS-FNRS, Brussels, Belgium). The MEG project at the CUB Hôpital Erasme is financially supported by the Fonds Erasme (Research grant “Les Voies du Savoir”, Brussels, Belgium).

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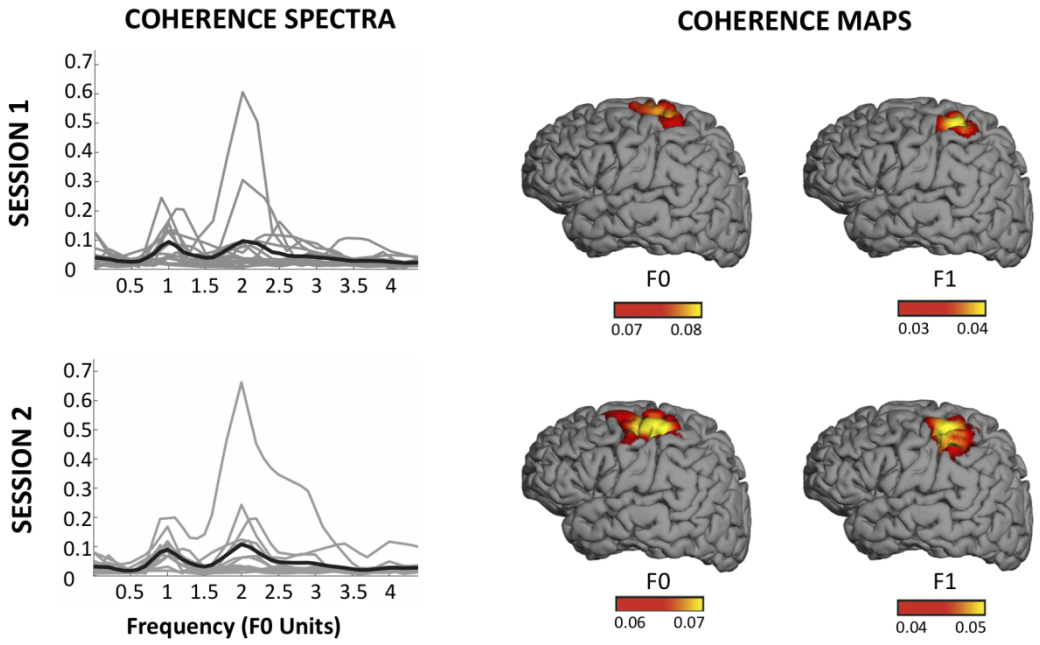
FIGURE LEGEND

Figure 1. CKC results obtained in *Active***. Left.** Individual sensor-level coherence spectra for each participant in *Active* for Session 1 (**Top**) and Session 2 (**Bottom**). Each gray trace

represents the coherence between magnetoencephalography (MEG) and accelerometer signals for each individual. For each frequency bin, the coherence value displayed is the maximum coherence across the MEG sensors covering the left rolandic MEG sensors. Black traces correspond to the group average. Frequencies are expressed in F0 units (i.e., 1 corresponds to the individual F0, 2 to its F1, etc.). **Right**. Group-level coherence maps in *Active* superimposed on left-hemisphere brain surface rendering. Group-level coherence maps for Session 1 (**Top**) and Session 2 (**Bottom**) at movement frequency (F0, **Left**) and its first harmonics (F1, **Right**).

F0 = movement frequency; F1 = first harmonics of movement frequency.


COHERENCE SPECTRA
COHERENCE MAPS
SESSION 1
SESSION 2
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.5 1 1.5 2 2.5 3 3.5 4
Frequency (F0 Units)
F0
0.07 0.08
F1
0.03 0.04
F0
0.06 0.07
F1
0.04 0.05