This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Marty, Brice; Gilles, Naeije; Bourguignon, Mathieu; Wens, Vincent; Jousmäki, Veikko; Lynch, David R; Gaetz, William; Goldman, Serge; Hari, Riitta; Pandolfo, Massimo; De Tiège, Xavier
Evidence for genetically determined degeneration of proprioceptive tracts in Friedreich ataxia

Published in:
Neurology

DOI:
[10.1212/WNL.00000000000007750](https://doi.org/10.1212/WNL.00000000000007750)

Published: 09/07/2019

Document Version
Publisher's PDF, also known as Version of record

Please cite the original version:

Marty, B., Gilles, N., Bourguignon, M., Wens, V., Jousmäki, V., Lynch, D. R., Gaetz, W., Goldman, S., Hari, R., Pandolfo, M., & De Tiège, X. (2019). Evidence for genetically determined degeneration of proprioceptive tracts in Friedreich ataxia. *Neurology*, 93(2), e116-e124. <https://doi.org/10.1212/WNL.00000000000007750>

Evidence for genetically determined degeneration of proprioceptive tracts in Friedreich ataxia

Brice Marty, PhD,* Gilles Naeije, MD, PhD,* Mathieu Bourguignon, PhD, Vincent Wens, PhD, Veikko Jousmäki, PhD, David R. Lynch, MD, PhD, William Gaetz, PhD, Serge Goldman, MD, PhD, Riitta Hari, MD, PhD, Massimo Pandolfo, MD, PhD, and Xavier De Tiège, MD, PhD

Neurology® 2019;93:e1-e9. doi:10.1212/WNL.0000000000007750

Correspondence

Dr. Naeije
Gilles.Naeije@
erasme.ulb.ac.be

Abstract

Objective

To assess with magnetoencephalography the developmental vs progressive character of the impairment of spinocortical proprioceptive pathways in Friedreich ataxia (FRDA).

Methods

Neuromagnetic signals were recorded from 16 right-handed patients with FRDA (9 female patients, mean age 27 years, mean Scale for the Assessment and Rating Of ataxia [SARA] score 22.25) and matched healthy controls while they performed right finger movements either actively or passively. The coupling between movement kinematics (i.e., acceleration) and neuromagnetic signals was assessed by the use of coherence at sensor and source levels. Such coupling, that is, the corticokinematic coherence (CKC), specifically indexes proprioceptive afferent inputs to the contralateral primary sensorimotor (cSM1) cortex. Nonparametric permutations and Spearman rank correlation test were used for statistics.

Results

In both groups of participants and movement conditions, significant coupling peaked at the cSM1 cortex. Coherence levels were 70% to 75% lower in patients with FRDA than in healthy controls in both movement conditions. In patients with FRDA, coherence levels correlated with genotype alteration (i.e., the size of GAA1 triplet expansion) and the age at symptom onset but not with disease duration or SARA score.

Conclusion

This study provides electrophysiologic evidence demonstrating that proprioceptive impairment in FRDA is mostly genetically determined and scarcely progressive after symptom onset. It also positions CKC as a reliable, robust, specific marker of proprioceptive impairment in FRDA.

RELATED ARTICLE

Editorial

Mapping proprioceptive function using corticokinematic coherence (CKC) in ataxias

Page 49

*These authors contributed equally to this work.

From the Laboratoire de Cartographie Fonctionnelle du Cerveau (B.M., G.N., M.B., V.W., S.G., X.D.T.) and Laboratoire Cognition Langage et Développement (M.B.), ULB Neuroscience Institute, and Department of Neurology (G.N., M.P.) and Department of Functional Neuroimaging (V.W., X.D.T., S.G.), Service of Nuclear Medicine, CUB Hôpital Erasme, Université libre de Bruxelles (ULB), Brussels, Belgium; Basque Center on Cognition, Brain and Language (M.B.), Donostia, Spain; Department of Neuroscience and Biomedical Engineering (V.J.), School of Science, Aalto University, Espoo, Finland; Children's Hospital of Philadelphia (D.R.L., W.G.), PA; and Department of Art (R.H.), Aalto University, Helsinki, Finland.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ANOVA = analysis of variance; **CKC** = corticokinematic coherence; **cSM1** = contralateral primary sensorimotor; **FRDA** = Friedreich ataxia; **FWHM** = full width at half-maximum; **FXN** = frataxin; **DRG** = dorsal root ganglia; **iSM1** = ipsilateral primary sensorimotor; **MEG** = magnetoencephalography; **PAM** = pneumatic artificial muscle; **SARA** = Scale for the Assessment and Rating of Ataxia; **SEP** = somatosensory evoked potential.

Friedreich ataxia (FRDA) is a rare autosomal recessive inherited ataxia mainly caused by expanded GAA triplet repeats in the first intron of the frataxin (FXN) gene (GAA1). GAA1 triplet expansion size correlates with age at onset and disease severity.¹ FRDA neuropathology affects dorsal root ganglia (DRG), posterior columns, and spinocerebellar tracts in the spinal cord, followed by progressive atrophy of the cerebellar dentate nuclei and efferent fibers,² leading to a tabeto-cerebellar ataxic pattern.³

Neuropathology and imaging studies show that DRG and spinal abnormalities occur very early and seem stable over time, leading to the onset and initial progression of ataxia.^{4,5} However, DRG in patients with long disease duration still show signs of active inflammation, supporting a continuing degenerative process.⁵ Dissecting the developmental from the progressive components of DRG and spinal pathology is therefore a critical issue for translational research in FRDA.⁶

Here, we used magnetoencephalography (MEG) and corticokinematic coherence (CKC) to address that issue by objectively assessing the function of proprioceptive ascending pathways in FRDA. CKC indexes the coupling between cortical activity and movement kinematics (e.g., acceleration) during repetitive voluntary^{7,8} and passive^{9,10} movements. CKC is driven by movement-related proprioceptive afferents to contralateral primary sensorimotor (cSM1) cortex^{10,11} and is relatively independent of movement rate.¹² Typically, CKC peaks at movement frequency and harmonics over cSM1 cortex.^{7–10} We expected CKC levels at cSM1 cortex to be substantially reduced in patients with FRDA and that they would correlate with GAA1 triplet expansion size, age at disease onset, clinical scores, or disease duration.

Methods

Participants

Sixteen patients with FRDA (mean age 27 years, range 9–46 years; 9 female and 7 male patients; mean Scale for the Assessment and Rating of Ataxia [SARA] score 21.4, range 9.5–30.5; mean GAA1 triplet expansion 670, range 280–1,000) and 16 healthy controls (mean age 29 years, range 10–53 years; 9 female controls) without a history of neuropsychiatric disease contributed to the study. Of note, 1 patient was heterozygous for a GAA1 repeat expansion and had a point mutation in the FXN gene.

Nine patients with FRDA (mean age 36 years, range 23–46 years; 5 female patients; mean SARA score 24, range 15.5–30.5;

mean GAA1 triplet expansion 621, range 280–910) also agreed to undergo somatosensory evoked potential (SEP) recording using electric stimulation of the right median nerve. Recording and analysis of SEPs were done as in the Naples cohort.¹³ except that, for comfort reasons, the 2 trials consisted of 256 rather than 1,000 epochs.

Ethics statement

All participants were included in the study after providing written informed consent. The study had prior approval by the CUB Hôpital Erasme Ethics Committee and was performed in accordance with the Declaration of Helsinki.

Experimental paradigm

The MEG experiment comprised three 5-minute conditions (active, passive, and rest) that were randomized across participants.

Figure 1 illustrates the 2 movement conditions used in this study.

In active, participants performed repetitive right index finger–thumb oppositions at a regular rate (≈ 2 Hz). Pauses were introduced if necessary.

In passive, a pneumatic artificial muscle (PAM) stimulator adapted from Piitulainen et al.¹¹ induced passive flexion–extensions of participants' right index finger at 3 Hz. This stimulator consisted of an elastic PAM (DMSP-10-100 AM-CM; Festo AG & Co, Esslingen, Germany) inserted horizontally in a polyoxymethylene cylinder on which participants could rest their hand. The PAM moved in the horizontal direction (5 mm of displacement) when its internal air pressure was varied (0–4 bars). The pressure was regulated by a solenoid valve (SY5220-6LOU-01F-Q, SMC Corp, Tokyo, Japan) that was controlled by the internal MEG-stimulator system.

In active and passive conditions, participants' finger movements were monitored with a 3-axis accelerometer (ADXL335 iMEMS Accelerometer, Analog Devices, Inc, Norwood, MA) attached to the nail of their right index finger.

In rest, participants were instructed to relax and not to move.

In all conditions, participants were instructed to gaze at a fixation point in the magnetically shielded room to avoid any eye movements or visual perception of the moving finger. They also wore earplugs to block the noise generated by finger movements or the PAM stimulator.

Figure 1 Movement conditions

(A) Passive condition. Illustration of the passive movements of the right index finger induced by the pneumatic artificial muscle (PAM) stimulator. During the experiments, the right index finger was taped to the moving extremity of the PAM stimulator. (B) One movement cycle in the active condition. An accelerometer was attached to the right index fingernail in both conditions.

Data acquisition

MEG signals were recorded with a whole-scalp-covering neuromagnetometer placed in a lightweight magnetically shielded room (Vectorview & Maxshield [Elekta Oy, Helsinki, Finland] for 10 patients and 4 healthy controls, and its upgraded version with similar sensor layout, the Triux & Maxshield [MEGIN, Helsinki, Finland], for 6 patients and 12 control individuals). MEG signals were filtered at 0.1 to 330 Hz and sampled at 1 kHz. Four head-tracking coils were used to monitor participants' head position inside the MEG helmet. The locations of the coils and at least 200 head-surface points (on scalp, nose, and face) with respect to anatomic fiducials were determined with an electromagnetic tracker (Fastrak, Polhemus, Colchester, VT) before MEG data acquisition. Acceleration signals were recorded time-locked to MEG with the use of a low pass at 330 Hz and a sampling rate of 1 kHz. High-resolution 3D T1 cerebral MRIs were acquired on a 1.5T MRI scanner (Intera, Philips, the Netherlands). Both MEG and MRI data were acquired at the CUB Hôpital Erasme.

Data preprocessing

Continuous MEG data were first preprocessed offline with the signal space separation method¹⁴ to suppress external interferences and to correct for head movements. Acceleration signal was computed at every time sample as the euclidian norm of the 3 band-passed accelerometer channels. Both MEG and accelerometer signals were split into 2-second epochs with 1.5-second overlap, leading to a spectral resolution of 0.5 Hz.¹⁵ Epochs within which the amplitude of MEG signals filtered through 0.1 to 145 Hz exceeded 3 pT (magnetometers) or 0.7 pT/cm (gradiometers) were marked as

artifact contaminated and rejected from further analysis. This procedure led to a similar number of epochs (patients with FRDA: active 665 ± 126 [mean $\pm$ SD], passive 667 ± 160 ; healthy controls: active 755 ± 52 , passive 655 ± 180) between conditions (analysis of variance [ANOVA], active vs passive $F_{1,15} = 1.09$, $p = 0.44$) and groups of participants (ANOVA, patients with FRDA vs healthy controls $F_{2,30} = 1.38$, $p = 0.26$).

Movement regularity

Movement regularity was quantified in the active condition for all participants. The principal component of the 3 high-passed (0.5 Hz) accelerometer signals was computed and then Fourier transformed. The resulting power spectrum was then smoothed with a gaussian kernel (full width at half-maximum [FWHM] 0.3 Hz). The first peak of the spectrum curve was then identified, and its FWHM was estimated. The former provided an estimate of movement frequency; the latter, an indicator of movement regularity (i.e., the smaller its value, the more regular the movements), at least under the hypothesis of movement stationarity. However, self-paced movement may present nonstationary drifts in movement frequency over the whole recording session while still being regular in the short term. Therefore, the global regularity index may lead to a false indication of irregularity. To take this possibility into account, we also estimated a short-time measure of regularity by computing the above FWHM index within 10-second-wide sliding windows and then averaging it over all windows.

Coherence analyses between accelerometer and MEG signals in sensor space

Coherence quantifies the degree of coupling between 2 signals by providing a number between 0 (no linear dependency) and

1 (perfect linear dependency) for each frequency.¹⁶ For each movement condition (active, passive), coherence between accelerometer and MEG signals was computed in sensor space^{7,10,17} to identify, without any a priori, the frequencies showing significant coupling between those signals. Frequencies showing consistent coherence across participants in sensor space were then defined as frequencies of interest for source-level analyses.

Coherence analyses in source space

MEG forward models and individual-level coherence maps were then computed in source space following a procedure detailed in previous studies from our group^{9–11} to obtain normalized coherence maps in the Montreal Neurological Institute space for each participant, condition (active, passive), and frequency of interest. Coherence maps at the group level were subsequently produced.^{9–11}

Statistical analyses

Sensor-space coherence at the individual level

The statistical significance of individual coherence levels was assessed under the hypothesis of linear independence.¹⁶ The significance threshold (C_t) is given by the following:

$$C_t = 1 - p^{1/(L-1)}$$

where p is the chosen significance level for individual channels and L is the number of disjoint epochs used for coherence estimation. The significance level was set to $p < 0.05$ Bonferroni corrected for multiple comparisons (i.e., 306 channels).

Statistical differences in movement frequency, movement regularity, and coherence levels in sensor space

Differences in movement frequency (active, passive) and regularity (active) between groups of participants (patients with FRDA vs healthy controls) were assessed with a 2-sample t test. The effects of group of participants, movement conditions, and frequencies of interest on maximal sensor-level coherence were assessed with 3-way repeated-measures ANOVA. Results were considered statistically significant at $p < 0.05$.

Source-space coherence at the group level

The statistical significance of local coherence maxima, identified in group-level coherence maps for each movement condition and frequency of interest, was assessed with a nonparametric permutation test,¹⁸ following the procedure described in reference 7. Statistical differences in group-level coherence maps in active and passive between healthy controls and patients with FRDA were assessed for each frequency of interest with a nonparametric permutation test similar to those previously described,⁷ with the only difference that group-level difference maps were obtained by subtracting healthy controls' Fisher-transformed active or passive coherence maps with the corresponding coherence maps of patients with FRDA.

Correlation analyses of individual source-space coherence values

Spearman rank correlation tests were used to seek for possible relations between the maximum coherence levels of patients with FRDA at the cSM1 cortex for each frequency of interest and the size of GAA1 triplet expansion, SARA score, age at onset of clinical symptoms, and disease duration. Of note, the patient with point mutation in the FXN gene was excluded from the correlations with GAA1 triplet expansion. Results were considered statistically significant at $p < 0.05$.

Data availability

Deidentified participant data will be shared, as well as the study protocol and statistical analyses, on request.

Results

Active condition

Despite identical instructions, patients with FRDA moved at a slower pace and less regularly than healthy controls (movement frequency [F0] 1.75 ± 0.5 vs 2.60 ± 1 Hz, $p = 0.03$; stationary movement regularity 1.20 ± 1.10 vs 0.64 ± 0.35 Hz, $p = 0.084$; short-time regularity 0.59 ± 0.14 vs 0.49 ± 0.07 Hz; $p = 0.016$).

Coherence at the sensor level

The table and figure 2 summarize sensor-level coherence results obtained in both groups of participants and movement conditions.

Statistically significant coherence peaked at F0 and its first harmonics (F1) in all healthy controls in the active condition and in all (F0) and 15 of 16 (F1) of them in the passive condition. All patients with FRDA displayed a significant coherence peak at F0, while 15 of 16 of them presented a significant coherence peak at F1 in the active condition. In the passive condition, significant coherence was found in 14 of 16 of patients with FRDA at F0 and in 8 of 16 of them at F1. In both groups of participants and conditions, coherence was maximal at central sensors contralateral to hand movements.

The 3-way ANOVA conducted on maximal sensor-level coherence disclosed a main effect of frequency of interest

Table Maximal coherence level at rolandic MEG sensors contralateral to finger movements

	Maximal coherence level (mean $\pm$ SD)			
	Active		Passive	
	F0	F1	F0	F1
Healthy controls	0.39 $\pm$ 0.18	0.40 $\pm$ 0.18	0.32 $\pm$ 0.18	0.13 $\pm$ 0.08
Patients with FRDA	0.12 $\pm$ 0.08	0.11 $\pm$ 0.12	0.14 $\pm$ 0.14	0.06 $\pm$ 0.08

Abbreviations: FRDA = Friedrich ataxia; MEG = magnetoencephalography.

Figure 2 Individual coherence spectra for each participant and movement condition

($F_{1,15} = 17.2, p = 0.001$), movement condition ($F_{1,15} = 27.2, p = 0.0001$), and participant group ($F_{1,15} = 20.3, p < 0.0001$), an interaction between frequency of interest and movement condition ($F_{1,15} = 10.5, p = 0.006$), and no other significant interaction ($F_{1,15} < 0.70, p > 0.77$). This pattern of results was explained by higher CKC values in healthy controls compared with patients with FRDA and lower CKC values at F1 than at F0 in the passive condition. On the basis of sensor-level coherence results, only F0 and F1 were considered for further source-space analyses.

Coherence at the source level

To identify the neuronal networks involved in coherence in active and passive conditions, similar coherence analyses were performed at the frequencies of interest (i.e., F0 and F1) at the source level. Figure 3 illustrates the results.

Active condition

In healthy controls, significant F0 and F1 coherence occurred at the cSM1 cortex with maximal amplitude over the hemisphere contralateral to hand movements (F0: Montreal Neurological Institute peak coordinates [−44 21 58] mm, coherence value 0.40; F1 [−43 23 60], 0.38). Of note, a clear but nonsignificant local coherence maximum was also observed at the ipsilateral primary sensorimotor (iSM1) cortex ([42 31 56], 0.10). In patients with FRDA, significant F0 coherence occurred at bilateral primary sensorimotor cortices with maximal amplitude over the hemisphere contralateral to hand movements (cSM1 cortex [−41 18 60], 0.10; iSM1 cortex [34 18 65], 0.08). Significant F1 coherence was also found only at the cSM1 cortex ([−45 22 57], 0.10). Coherence at F0 and F1 over the cSM1 cortex

(F0 [−48 29 56]; F1 [−36 17 64]) was significantly higher in healthy controls than in patients with FRDA (F0: 0.4 vs 0.10; F1: 0.38 vs 0.1).

Passive condition

In healthy controls and patients with FRDA, significant F0 and F1 coherence occurred at cSM1 cortex (healthy controls, F0 [−45 21 58], 0.3/F1 [−47 25 57], 0.10; patients with FRDA, F0 [−48 19 54], 0.10/F1 [−49 20 51], 0.04). At F0, coherence levels at cSM1 cortex were significantly lower in patients with FRDA compared with healthy controls (F0 [−33 to 14 68], 0.10 vs 0.30), while no significant difference was observed at F1.

Correlation analyses

In patients with FRDA with GAA1 triplet expansion (15 of 16 patients with FRDA), levels of cSM1 cortex coherence in active F1 correlated with the age at onset ($r = 0.75, p = 0.004$) and with the size of GAA1 triplet expansion ($n = 15; r = -0.67, p = 0.001$). In the passive condition, levels of F1 cSM1 cortex coherence correlated only with the size of GAA1 triplet expansion ($n = 15; r = -0.59, p = 0.009$). No other correlation appeared significant. Figure 4 illustrates those correlations. Of note, when the 2 patients with the shortest GAA1 who are associated with the highest corticokinematic coherence (CKC) values at F1 are removed from the analyses, correlations remain (nGAA1, active: $r = -0.66, p = 0.014$, passive: $r = -0.56, p = 0.047$; age at onset, active: $r = 0.56, p = 0.047$).

Somatosensory evoked potentials

N20 response was clearly identified in only 2 of 9 of the patients with FRDA who underwent classic SEP testing, with

Figure 3 Group-level coherence maps superimposed on brain surface rendering

All maps are thresholded at statistically significant coherence level (lower bound of the color scale, permutation-based statistics). Brain is viewed from the top. Group-level coherence maps for healthy controls and patients with Friedreich ataxia (FRDA) in (A) active and (B) passive conditions at movement frequency (F0) and its first harmonics (F1). Difference in group-level coherence maps between healthy controls and patients with FRDA in active and passive conditions at F0 and F1. Enlarged area highlights the significant difference at F0 in the passive condition.

latencies of 26.1 milliseconds and 27.7 milliseconds and amplitudes of 0.3 and 0.4 μV (normal values of the Clinical Neurophysiology Department of the CUB Hôpital Erasme for N20 latency and amplitude: 19.6 ± 1.0 milliseconds and 2.1 ± 0.9 μV , respectively).

Discussion

This study demonstrates that (1) the coupling between index-finger movement kinematics and cSM1 cortex neuromagnetic activity is reduced in patients with FRDA compared with healthy controls matched for age and sex during both active and passive finger movements, (2) CKC is a more reliable measure than SEPs in patients with FRDA, and (3) the level of coherence at cSM1 cortex in patients with FRDA correlates with the size of GAA1 triplet expansion in both active and passive at F1 but not with the SARA score or disease duration. These findings provide empirical evidence supporting that the severity of spinocortical proprioceptive pathway degeneration in FRDA is genetically determined and has little tendency to progress after disease onset. They also validate CKC as a specific and robust electrophysiologic marker of spinocortical proprioceptive pathway degeneration in FRDA.

Previous CKC studies performed in healthy controls demonstrated that CKC is robustly observed at the cSM1 cortex at

the individual level during both active^{7,8,17} and passive^{10,11} finger movements. Furthermore, they highlighted that CKC is driven by movement-related proprioceptive afferent input to the cSM1 cortex with negligible influence of tactile input.^{10,11} A longitudinal study performed in a similar population also demonstrated that CKC levels at cSM1 cortex are fairly reproducible across sessions.¹⁹ All these findings set the rationale for using CKC to obtain an objective, reliable, and specific measure of proprioceptive pathways impairment in patients with FRDA. The working hypothesis guiding the present study was that the use of CKC would bring novel insights into FRDA pathophysiology and, more particularly, into the developmental vs the degenerative character of proprioceptive pathways impairment in this disorder.

As expected, in both active and passive conditions, CKC levels were substantially decreased in patients with FRDA (decrease by about two thirds or three quarters of the values in healthy controls). Furthermore, a negative correlation was found in both movement conditions between CKC levels at F1 and the size of GAA1 triplet expansion. These findings therefore imply that the low CKC levels observed in patients with FRDA are actually the consequence of an early and scarcely progressive, possibly developmental, pathology of spinocortical proprioceptive pathways. These results also imply that whenever genetic therapy to restore DRG and medullary

Figure 4 Correlations analysis

Plot of the Spearman correlation between individual CKC levels at F1 of patients with FRDA in the active condition and size of GAA1 triplet expansion on the shortest allele (nGAA1) (A) or the age at onset (B) and between individual CKC levels at F1 in patients with FRDA in the passive condition and the size of GAA1 triplet expansion on the shortest allele (nGAA1) (C).^{33–35} FRDA = Friedreich ataxia.

posterior column FXN level becomes available, it should be started as early as possible at the preclinical stage. However, an early proprioceptive pathology, possibly even hypoplasia, does not imply that the remaining somatosensory neurons responsible for residual proprioception in patients with FRDA would not degenerate with time and contribute to the progressive worsening of ataxia. However, CKC data indicate that, in the course of FRDA, the ongoing loss of proprioception is likely to be minor compared with cerebellar and pyramidal degenerations.^{2,20} Longitudinal CKC investigations along the course of FRDA could help to clarify the existence of subtle progressive dysfunction of the posterior column and to assess the potential yield of early therapeutic intervention to alleviate symptoms of the proprioceptive impairment. Still, the lack of correlation of CKC levels at the cSM1 cortex and disease duration does not support this hypothesis.

Previous studies have demonstrated that SEPs are not reliably identified between one-third and two-thirds of patients with FRDA.^{13,21–26} Our finding that SEPs were visible in only 2 of 9 patients with FRDA is in line with those data. In the Naples cohort¹⁵ in whom SEPs were detectable in 36 of 52 patients, patients with FRDA had similar GAA1 repeat expansions (621 ± 225 for CUB Hôpital Erasme vs 661 ± 257 for Naples) but different disease durations (20 ± 11 vs 10 ± 7 years). However, the difference in disease duration is not likely to account for the discrepancy between our rates of recordable SEPs because in the Naples cohort N20 amplitude did not correlate with disease duration. A possible explanation for the better sensitivity of SEPs in the Naples cohort could be that, to record SEPs, those investigators averaged the neural responses elicited by 2,000 electric stimuli on each side,¹⁵ while we limited the number of electric stimuli on each side to 512, meaning that their signal-to-noise ratio was 2 times ours. Still, despite the frequent absence of SEPs in patients with FRDA, CKC was reliably recorded in all (active) or almost all (passive) patients, even when SEPs were not detectable. When measurable, the amplitude of N20 responses obtained in previous studies tended to be stable over time and correlated with the size of GAA1 triplet expansion, while the correlation with disease progression varied across studies.^{13,22–25,27}

These findings indicate that the loss of N20 and the reduction of CKC levels share similar disease-related impairment of the somatosensory system. However, because CKC can be measured in almost all patients with FRDA, it appears as a robust, more reliable, and specific marker than SEP recordings to assess the pathology of proprioceptive pathways in FRDA. Patients with FRDA who are compound heterozygotes (GAA expansion and an FXN point mutation) display the same mixed afferent and cerebellar ataxia phenotype as homozygous patients with FRDA with GAA triplet expansion,²⁸ so CKC can be used to assess spinocortical proprioceptive pathways alteration in these patients also. Results also suggest that CKC could be of great interest to assess impairment of proprioceptive pathways in various diseases affecting the posterior columns of the spinal cord such as multiple sclerosis,²⁹ vitamin B₁₂ deficiency,³⁰ stroke,³¹ and medullary compression.³² Such studies would also inform about the specificity of the CKC alterations in different patient groups, including patients with FRDA. Finally, in FRDA and other genetic spinocerebellar ataxias, CKC could potentially serve to identify preclinical stages in patients in whom a genetic diagnosis was made. Indeed, in most common spinocerebellar ataxias (1, 2, 3, and 6) and in FRDA, genotypic anomalies predict only a part of age-at-onset variability, disease severity, and survival.^{33–35} On the other hand, in spinocerebellar ataxias, SEPs are altered as early as 8 years before symptom onset (for a review, see reference 36), which suggests that CKC, as a robust method, might help to sort presymptomatic patients and therefore play a role in the determination of the optimum time for early therapeutic intervention.

That patients with FRDA moved at a slower pace and less regularly than healthy controls in the active condition is

unlikely to explain the difference in CKC levels observed between the 2 groups. Indeed, CKC levels in active and passive conditions were similar at F0 in both groups of participants and stronger in the active condition at F1 in patients with FRDA. This (expectable) difference in movement characteristics between patients with FRDA and healthy controls justifies the importance of the passive condition. The interest in the use of a metronome to pace active movements should be addressed in future studies. In active and passive conditions, CKC peaked at F0 and F1 over the cSM1 cortex in both groups of participants, which is in line with previous CKC studies performed in healthy individuals.^{7,9,10} Our finding that, in the active condition, local CKC maxima at the iSM1 cortex were significant only in patients with FRDA is explained by the statistical approach used in this study. Indeed, permutation tests may be too conservative (type II error) for voxels other than those with high coherence levels.¹⁸ In patients with FRDA, CKC levels at cSM1 cortex were much lower than those observed in healthy controls, explaining why CKC levels at the iSM1 cortex appeared significant in patients with FRDA and not in healthy controls.

The neural bases of CKC at F0 and F1 are still debated. Either F0 and F1 CKC may reflect cortical processing of different movement kinematics features, or F1 may be due to nonsinusoidal cortical activity at F0, leading to coherence at twice F0.⁷ In repetitive index-finger movements such as those used in this study, F0 is likely to reflect cycles of index finger flexions/extensions and corresponding proprioceptive signals, while F1 might reflect the contraction/relaxation of agonist and antagonist muscles during both flexion and extension. This difference between F0 and F1 CKC might explain why the CKC levels at cSM1 cortex of patients with FRDA correlated with the size of GAA1 triplet expansion and the age at onset better at F1 than at F0. In addition, the absence of a significant difference between healthy controls and patients with FRDA at F1 in the passive condition is probably related to the relatively weak coherence at F1 observed in healthy controls and to the variability of this frequency in patients with FRDA.

FRDA is a complex neurogenetic disorder that involves mainly degeneration of proprioceptive afferent and cerebellar pathways. Clinical rating scales are able to capture the progression of cerebellar impairment, but the involvement of proprioceptive pathways is less well quantified clinically, hence the need for robust markers of proprioceptive impairment. We provided electrophysiologic evidence that spinocortical proprioceptive impairment in FRDA is mostly genetically determined and scarcely progressive after symptom onset. We also demonstrate that CKC represents a reliable and robust individual-level marker of spinocortical proprioceptive loss in FRDA. CKC may therefore represent a useful addition to the armamentarium of FRDA clinical evaluation to assess the natural history of this disorder and the efficacy of dedicated early therapeutic approaches.

Study funding

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 (Brussels, Belgium; research credit: J.0095.16.F), and a research grant from the Friedreich Ataxia Research Alliance (Drs. Pandolfo, Gaetz, and Lynch). Gilles Naeije was supported by a research grant from the Fonds Erasme (Brussels, Belgium). Mathieu Bourguignon was supported by the program Attract of Innoviris (grant 2015-BB2B-10), by the Spanish Ministry of Economy and Competitiveness (grant PSI2016-77175-P), and by the Marie Skłodowska-Curie Action of the European Commission (grant 743562). Xavier De Tiège and Gilles Naeije are Postdoctorate Clinical Master Specialists at the Fonds de la Recherche Scientifique (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). The accelerometer and PAM stimulator were designed and manufactured at Aalto NeuroImaging, Aalto University, Finland.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* September 27, 2018. Accepted in final form February 25, 2019.

Appendix Authors

Name	Location	Role	Contribution
Gilles Naeije, MD, PhD	Université libre de Bruxelles (ULB), Brussels, Belgium	Author	Designed and conceptualized study; conducted the experiments; analyzed the data; wrote the manuscript; designed figure 4; wrote the revisions.
Brice Marty, PhD	Université libre de Bruxelles (ULB), Brussels, Belgium	Author	Conducted the experiments; analyzed the data; contributed to the writing of Methods, Results, and figures 1 through 3 legends; designed figures 1 through 3.
Mathieu Bourguignon, PhD	Université libre de Bruxelles (ULB), Brussels, Belgium	Author	Analyzed the data; drafted the manuscript for intellectual content.
Vincent Wens, PhD	Université libre de Bruxelles (ULB), Brussels, Belgium	Author	Analyzed the data; drafted the manuscript for intellectual content.
Veikko Jousmäki, PhD	School of Science, Aalto University, Espoo, Finland	Author	Designed and provided the PAM stimulator; provided input for research design and interpretation; drafted the manuscript for intellectual content.

Appendix (continued)

Name	Location	Role	Contribution
David R Lynch, MD, PhD	Children's Hospital of Philadelphia, PA	Author	Drafted the manuscript for intellectual content.
William Gaetz, PhD	Children's Hospital of Philadelphia, PA	Author	Provided input for research design and interpretation; drafted the manuscript for intellectual content.
Serge Goldman, MD, PhD	Université libre de Bruxelles (ULB), Brussels, Belgium	Author	Drafted the manuscript for intellectual content; provided input for research design and interpretation.
Riitta Hari, MD, PhD	Department of Art, Aalto University, Helsinki, Finland	Author	Drafted the manuscript for intellectual content; provided input for research design and interpretation.
Massimo Pandolfo, MD, PhD	Université libre de Bruxelles (ULB), Brussels, Belgium	Author	Designed and conceptualized the study; drafted the manuscript for intellectual content; provided input for research design and interpretation.
Xavier De Tiège, MD, PhD	Université libre de Bruxelles (ULB), Brussels, Belgium	Author	Designed and conceptualized the study; wrote the manuscript; drafted the manuscript for intellectual content; provided input for research design and interpretation; contributed to the revisions.

References

- Campuzano V, Montermini L, Molto MD, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science* 1996;271:1423–1427.
- Koeppen AH, Mazurkiewicz JE. Friedreich ataxia: neuropathology revised. *J Neuropathol Exp Neurol* 2013;72:78–90.
- Pandolfo M. Friedreich ataxia. *Arch Neurol* 2008;65:1296–1303.
- Mascalchi M, Bianchi A, Ciulli S, et al. Lower medulla hypoplasia in Friedreich ataxia: MR imaging confirmation 140 years later. *J Neurol* 2017;264:1526–1528.
- Koeppen AH, Ramirez RL, Becker AB, Mazurkiewicz JE. Dorsal root ganglia in Friedreich ataxia: satellite cell proliferation and inflammation. *Acta Neuropathol Commun* 2016;4:46.
- Piguet F, de Montigny C, Vaucamps N, Reutenauer L, Eisenmann A, Puccio H. Rapid and complete reversal of sensory ataxia by gene therapy in a novel model of Friedreich ataxia. *Mol Ther* 2018;26:1940–1952.
- Bourguignon M, Jousmäki V, Op de Beeck M, Van Bogaert P, Goldman S, De Tiège X. Neuronal network coherent with hand kinematics during fast repetitive hand movements. *Neuroimage* 2012;59:1684–1691.
- Piitulainen H, Bourguignon M, De Tiège X, Hari R, Jousmäki V. Coherence between magnetoencephalography and hand-action-related acceleration, force, pressure, and electromyogram. *Neuroimage* 2013;72:83–90.
- Bourguignon M, Piitulainen H, De Tiège X, Jousmäki V, Hari R. Corticokinematic coherence mainly reflects movement-induced proprioceptive feedback. *Neuroimage* 2015;106:382–390.
- Piitulainen H, Bourguignon M, De Tiège X, Hari R, Jousmäki V. Corticokinematic coherence during active and passive finger movements. *Neuroscience* 2013;238:361–370.
- Piitulainen H, Bourguignon M, Hari R, Jousmäki V. MEG-compatible pneumatic stimulator to elicit passive finger and toe movements. *Neuroimage* 2015;112:310–317.
- Marty B, Bourguignon M, Op de Beeck M, et al. Effect of movement rate on corticokinematic coherence. *Neurophysiol Clin Neurophysiol* 2015;45:469–474.
- Santoro L, Perretti A, Lanzillo B, et al. Influence of GAA expansion size and disease duration on central nervous system impairment in Friedreich's ataxia: contribution to the understanding of the pathophysiology of the disease. *Clin Neurophysiol* 2000;111:1023–1030.
- Taulu S, Simola J, Kajola M. Applications of the signal space separation method. *IEEE Trans Sign Proc* 2005;53:3359–3372.
- Bortel R, Sovka P. Regularization techniques in realistic laplacian computation. *IEEE Trans Biomed Eng* 2007;54:1993–1999.
- Halliday DM, Rosenberg JR, Amjad AM, Breeze P, Conway BA, Farmer SF. A framework for the analysis of mixed time series/point process data: theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. *Prog Biophys Mol Biol* 1995;64:237–278.
- Marty B, Bourguignon M, Jousmäki V, et al. Cortical kinematic processing of executed and observed goal-directed hand actions. *Neuroimage* 2015;119:221–228.
- Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp* 2002;15:1–25.
- Piitulainen H, Illman M, Laaksonen H, Jousmäki V, Forss N. Reproducibility of corticokinematic coherence. *Neuroimage* 2018;179:596–603.
- Cruz-Martinez A, Palau F. Central motor conduction time by magnetic stimulation of the cortex and peripheral nerve conduction follow-up studies in Friedreich's ataxia. *Electroencephalogr Clin Neurophysiol* 1997;105:458–461.
- Santiago-Perez S, Perez-Conde MC, Ugalde-Canitrot A, Lopez-Pajares MR. A neurophysiological study of the alterations to the central and peripheral nervous systems in Friedreich's ataxia. *Rev Neurol* 2007;44:193–197.
- Santoro L, De Michele G, Perretti A, et al. Relation between trinucleotide GAA repeat length and sensory neuropathy in Friedreich's ataxia. *J Neurol Neurosurg Psychiatry* 1999;66:93–96.
- Vanasse M, Garcia-Larrea L, Neuschwander P, Trouillas P, Mauguère F. Evoked potential studies in Friedreich's ataxia and progressive early onset cerebellar ataxia. *Can J Neurol Sci* 1988;15:292–298.
- Ouvrier RA, McLeod JG, Conchin TE. Friedreich's ataxia: early detection and progression of peripheral nerve abnormalities. *J Neurol Sci* 1982;55:137–145.
- Pelosi L, Fels A, Petrillo A, et al. Friedreich's ataxia: clinical involvement and evoked potentials. *Acta Neurol Scand* 1984;70:360–368.
- Jones SJ, Baraitser M, Halliday AM. Peripheral and central somatosensory nerve conduction defects in Friedreich's ataxia. *J Neurol Neurosurg Psychiatry* 1980;43:495–503.
- Santoro L, Perretti A, Crisci C, et al. Electrophysiological and histological follow-up study in 15 Friedreich's ataxia patients. *Muscle Nerve* 1990;13:536–540.
- Cossée M, Dürr A, Schmitt M, et al. Friedreich's ataxia: point mutations and clinical presentation of compound heterozygotes. *Ann Neurol* 1999;45:200–206.
- Ganes T. Somatosensory evoked responses and central afferent conduction times in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1980;43:948–953.
- Zegers de Beyl D, Delecluse F, Verbanck P, Borenstein S, Capel P, Brunko E. Somatosensory conduction in vitamin B12 deficiency. *Electroencephalogr Clin Neurophysiol* 1988;69:313–318.
- Tinazzi M, Mauguère F. Assessment of intraspinal and intracranial conduction by P30 and P39 tibial nerve somatosensory evoked potentials in cervical cord, brainstem, and hemispheric lesions. *J Clin Neurophysiol* 1995;12:237–253.
- Miyoshi T, Kimura J. Short-latency somatosensory evoked potentials in patients with cervical compressive lesions: morphological versus functional examination. *Electromyogr Clin Neurophysiol* 1996;36:323–332.
- 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.
- van de Warrenburg BPC, Hendriks H, Dürr A, et al. Age at onset variance analysis in spinocerebellar ataxias: a study in a Dutch-French cohort. *Ann Neurol* 2005;57:505–512.
- Reetz K, Dogan I, Costa AS, et al. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. *Lancet Neurol* 2015;14:174–182.
- Maas RP, van Gaalen J, Klockgether T, van de Warrenburg BP. The preclinical stage of spinocerebellar ataxias. *Neurology* 2015;85:96–103.

Neurology®

Evidence for genetically determined degeneration of proprioceptive tracts in Friedreich ataxia

Brice Marty, Gilles Naeije, Mathieu Bourguignon, et al.

Neurology published online June 13, 2019

DOI 10.1212/WNL.0000000000007750

This information is current as of June 13, 2019

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/early/2019/06/13/WNL.0000000000007750.full
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Clinical Neurology http://n.neurology.org/cgi/collection/all_clinical_neurology Gait disorders/ataxia http://n.neurology.org/cgi/collection/gait_disorders_ataxia Spinocerebellar ataxia http://n.neurology.org/cgi/collection/spinocerebellar_ataxia Trinucleotide repeat diseases http://n.neurology.org/cgi/collection/trinucleotide_repeat_diseases
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2019 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.