RESEARCH ARTICLE

Individual Changes in Preclinical Spinocerebellar Ataxia Identified Via Increased Motor Complexity

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ABSTRACT: Background: Movement changes in autosomal-dominant spinocerebellar ataxias are suggested to occur many years before clinical manifestation. Detecting and quantifying these changes in the preclinical phase offers a window for future treatment interventions and allows the clinician to decipher the earliest dysfunctions starting the evolution of spinocerebellar ataxia. We hypothesized that quantitative movement analysis of complex stance and gait tasks allows to (i) reveal movement changes already at early stages of the preclinical phase when clinical ataxia signs are still absent and to (ii) quantify motor progression in this phase.

Methods: A total of 46 participants (14 preclinical spinocerebellar ataxia mutation carriers [spinocerebellar ataxias 1,2,3,6], 9 spinocerebellar ataxia patients at an early stage; 23 healthy controls) were assessed by quantitative movement analyses of increasingly complex stance and walking tasks in a cross-sectional design.

Results: Body sway in stance and spatiotemporal variability in tandem walking differentiated between preclinical mutation carriers and healthy controls ($P<.01$). Complex movement conditions allowed one to discriminate even those mutation carriers without any clinical signs in posture and gait ($SARA_{posture\&gait}=0$; $P<.04$). Multivariate regression analysis categorized preclinical mutation carriers on a single-subject level with 100% accuracy within a range of 10 years to the estimated onset. Movement features in stance and gait correlated significantly with genetically estimated time to onset, indicating a gradual increase of motor changes with increasing proximity to disease manifestation.

Conclusion: Our results provide evidence for subclinical motor changes in spinocerebellar ataxia, which allow to discriminate patients without clinical signs even on a single-subject basis and may help capture disease progression in the preclinical phase. © 2016 International Parkinson and Movement Disorder Society

Key Words: spinocerebellar ataxia; preclinical stage; movement analysis; quantitative motor features; multivariate analysis

It is well known from various neurodegenerative diseases such as Parkinson's disease or Huntington's disease that, at the point of clinical manifestation, large populations of underlying neurons are already lost and most compensatory resources are already exhausted.[1-3] The same is likely true also for cerebellar functioning in degenerative spinocerebellar ataxias (SCAs).[4-6] The preclinical phase of SCAs attracts increasing research interest as it could provide a promising window for early therapeutic intervention before substantial irreversible neurodegeneration has occurred.[4,5,7] The effectiveness of future interventions studies in SCAs will largely depend on the following 3 prerequisites: (1) Detection and quantification of motor control deficits as early as possible, (2) a more detailed understanding of the earliest dysfunctions in cerebellar motor control mechanisms starting the evolution of

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TABLE 1. Description of participants

Groups	No. of participants	Age, y	Gender (F/M)	SARA	$SARA_{p\&g}$	INAS II	Estimated disease onset, y: $eT2DO^{CAG}$	Estimated disease onset, y: $eT2DO^{CAG}_{par}$	SCA type # (1,2,3,6)
$SCA^{SARA3-8}$	9	40.5 (13.3) [20-68]	4/5	5.1 (1.3) [3-8]	2.1 (1.6) [0-4]	3.3 (2) [1-8]	n.a.	n.a.	5,1,2,1
$MC^{SARA<3}$	14	(13.3) [24-65]	6/8	1.21 (0.9) [0-2.5]	0.21 (0.4) [0-1]	0.7 (0.7) [0-2]	9.5 [0.4-20.3]	6.07 [0.9-15]	5,2,3,4
$MC^{SARAp\&g=0}$	8	44.9 (5.3) [24-65]	5/3	0.5 (0.46) [0-1]	[0-0]	0.8 (0.8) [0-2]	8.25 [0.4-12]	7.6 [1.6-15]	3,0,1,4
nMC	8	43.8 (16.3) [20-60]	4/4	0.56 (0.7) [0-2]	[0-0]	0.5 (0.5) [0-1]	n.a.	n.a.	n.a.
HC	23	40.5 (13) [20-66]	11/12	0.33 (0.5) [0-2]	[0-0]	n.a.	n.a.	n.a.	n.a.

Given are averages or mean values, standard deviations, and ranges. Ataxia symptoms were clinically assessed using SARA. SARA covers a range from 0 (no ataxia) to 40 (most severe ataxia). The SARA score includes the following 8 items: 3 items rating gait and posture, 1 item for speech disturbances, and 4 items for limb-kinetic functions. The 3 items rating gait and posture are summarized in the gait&posture subscore ($SARA_{p\&g}$). The groups $MC^{SARA<3}$ and HC differed significantly in SARA scores ($P = .002$). In contrast, the $MC^{SARAp\&g=0}$ and nMC groups did not differ in SARA score ($P = .97$), INAS score ($P = .5$) or age ($P = .98$), and in both groups none of the participants showed clinical gait and posture abnormalities. For individual INAS scores, see Supplement 3. $SCA^{SARA3-8}$, patients with SCA 1,2,3 or 6 in the early clinical stage of the disease with a SARA score of 3-8; $MC^{SARA<3}$, preclinical mutation carriers of SCA 1, 2, 3, and 6 with a SARA score of <3; $MC^{SARAp\&g=0}$, subgroup of the preclinical mutation carrier group, all with a $SARA_{posture\&gait}$ subscore = 0 and SARA total score of ≤1; nMC, subgroup of healthy, age-matched controls consisting of first-degree relatives of SCA patients tested negative for the mutation; HC, healthy controls; n.a., not applicable; INAS, Inventory of Non-Ataxia Signs[27] (see supplement for details of scores); SARA, scale for the assessment and rating of ataxia; SCA, spinocerebellar ataxia; $eT2DO^{CAG}$, genetically estimated timespan (years) to clinical disease onset, according to [28]; $eT2DO^{CAG}_{par}$, genetically estimated time to clinical disease onset, adjusted by parental disease of onset (see Equation 1); SCA(1,2,3,6), number of patients with spinocerebellar ataxia type 1,2,3,6.
#Number of participants in each group.

ataxia, (3) the availability of measures that are able to sensitively quantify progression and intervention benefits in this preclinical stage.

First studies have recently started to investigate presymptomatic persons at risk for SCA,[4,6] focusing mainly on clinical ataxia scores such as the Scale for the Assessment and Rating of Ataxia (SARA)[8] as a primary measure. However, by their nature, clinical scores lack the sensitivity to identify subtle movement changes and to quantify the progression in the preclinical phase.[9] Nonclinical measures might thus outperform clinical ataxia scores for identifying and quantifying signs during the preclinical phase of SCA. Quantitative motor measures of posture and gait seem particularly promising for finding a unifying description of preclinical motor symptoms across SCA subtypes, as clinical observation shows that coordinatively demanding gait and stance tasks, such as tandem gait and stance, are abnormal already very early in the clinical disease course. In fact, gait difficulties have been identified as the first symptom in two thirds of 287 patients across all the main SCA genotypes 1, 2, 3, and 6.[10] Finding such a SCA-unifying signature of the preclinical phase might complement (or partly even overtake) early nonataxia symptoms such as muscle cramps, oculomotor signs, and sleep disturbances or brain imaging abnormalities,[4,6,11,12] which seem largely specific to certain SCA subtypes.[5]

The hypothesis of quantitative motor measures as a promising early marker for characterizing the preclinical phase of SCA is based on earlier studies on quantification of spatiotemporal movement features in SCAs. It has been shown that movement measures of spatial and temporal variability are distinctively suitable for characterizing ataxic gait,[13-17] including in mild ataxic and subclinical patients.[13,18,19] In addition, these measures are particularly attractive because they allow also for a fine-grained quantification of treatment effects in degenerative ataxias.[20-23]

Here we hypothesized that (i) quantitative movement features might be able to identify movement changes already at early stages of the preclinical phase across SCA subtypes, when clinical signs of ataxia are still absent. Moreover, we speculated that (ii) these movement features might also help quantify the progression of motor deficits in the preclinical phase before disease onset.

Methods

Participants

We recruited 3 subject groups: a group of 14 preclinical mutation carriers with a repeat expansion mutation in the genes causing SCA 1, 2, 3, or 6 with a SARA score of <3 ($MC^{SARA<3}$); a group of 9 patients with SCA 1, 2, 3, or 6 in the early clinical stage (SARA score 3-8; $SCA^{SARA3-8}$); and a group of 23 age- and gender-matched healthy controls (HCs; see Table 1). In line with previous studies on preclinical SCA,[4,5] the cutoff value between preclinical mutation carriers ($MC^{SARA<3}$) versus patients with manifest SCA ($SCA^{SARA3-8}$) was set at a SARA score of 3. HC included 10 members of SCA 1, 2, 3, or 6 families who were shown to have not inherited the SCA mutation. The other 13 HCs had no personal or family history of any neurological or psychiatric disease. None of the HCs showed any neurological signs upon clinical examination.

To investigate more strictly whether movement analysis helps identify motor changes in the early preclinical stages when any clinical signs in posture and gait control are indeed still completely absent, we formed an additional subgroup out of the $MC^{SARA<3}$ group, selecting only those patients with a $SARA_{posture\&gait}$ subscore = 0 ($SARA_{posture\&gait}$ = sum of the 3 SARA items: gait, stance, and sitting)[8,24] and a SARA total score ≤1 (n = 8 patients total; $MC^{SARAp\&g=0}$). Because

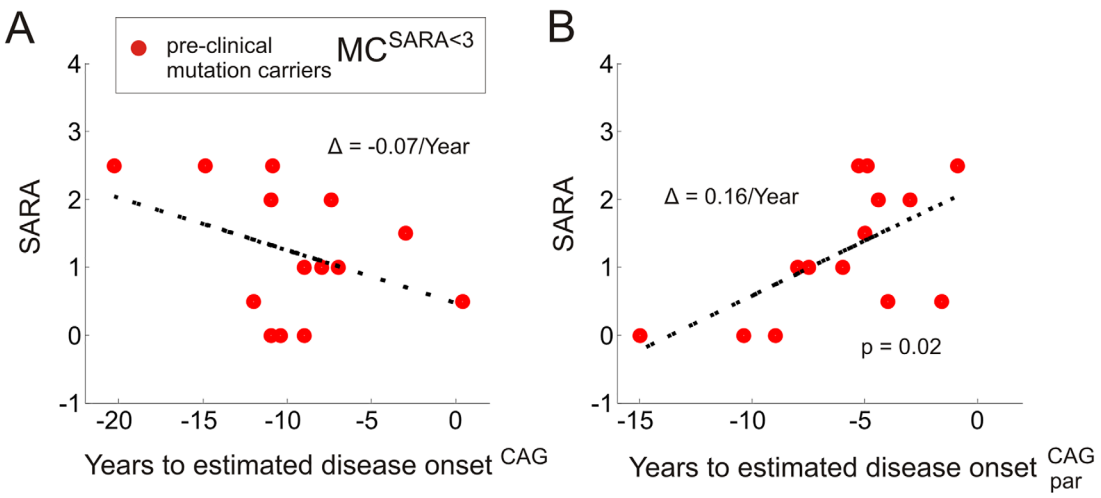

FIG. 1. Relationships between estimated time to disease onset and the scale for the assessment and rating of ataxia (SARA) scores in the preclinical mutation carriers of spinocerebellar ataxia (SCA) 1, 2, 3, and 6 with a SARA score of <3 ($MC^{SARA<3}$) cohort, with time to disease onset calculated by the unadjusted model[28] (**A**) and the parentally adjusted model (**B**; see Equation 1). The adjusted model modifies the estimated onset in particular for those patients with >10 years to disease onset and incipient clinical signs (SARA>1). The black lines denote linear fits of the data; the averaged changes per year are indicated by Δ. The *P* value indicates a significant correlation between durations to estimated disease onset and the SARA score. [Color figure can be viewed at wileyonlinelibrary.com]

this $MC^{SARAp\&g=0}$ subgroup differed in age from the HCs and because age is known to modulate balance and gait capacities,[25,26] we defined an age-matched subgroup of the HCs, selecting 8 age-matched mutation-negative family members of SCA patients (nonmutation carriers [nMC]), thus helping to control for unspecific features that might be present in SCA families. Neurological signs other than ataxia were assessed with the Inventory of Non-Ataxia Signs.[27]

Genetics

All mutation carriers carried repeat expansions in the clearly pathological, fully penetrant range. Cytosine Alanine Guanine (CAG) repeat length was analyzed in the DNA extracted from ethylenediamine tetraacetic acid (EDTA) blood samples at the Institute of Medical Genetics and Applied Genomics, University of Tübingen, using well-established methods[4,28] (for further details see Supplement 5).

Standard Protocol Approvals and Patient Consents

All experimental procedures were approved by the local ethics committee (Az303/2008BO2). All participants gave written informed consent. No descriptive single-participant data about individual age, allele sizes, or genotypes are shown in the manuscript because this might allow participants to reidentify themselves and to recognize her or his genotype status. Means and standard deviation of CAG repeat lengths are provided in Supplement 4.

Estimation of Disease Onset

Movement features of the $MC^{SARA<3}$ patients were related to the genetically estimated disease onset, which was calculated according to the previously established model[28] (= unadjusted model). This estimate is based on the genotype, number of CAG repeats, and age of the participant. However, it is known that the mutant CAG repeat allele explains only 60% of the age of onset variance.[29] About 55% of the remaining age-of-onset variance is a result of familial factors.[29,30] These factors probably consist of a number of cis- and trans-acting genetic modifiers and share familial environmental factors that influence age of onset in addition to the expanded CAG repeat allele itself.[29,31] To account for these intrafamilial effects, we adjusted the CAG-based age-of-onset estimation of the index participant by the difference between the actual disease onset and the CAG-based age of onset estimation in the affected parent (Equation 1; adjusted model).

$$\begin{aligned} &estimated\ disease\ onset^{CAG}_{par} \\ &= estimated\ disease\ onset^{CAG} \\ &+[actual\ disease\ onset(parent) \\ &-estimated\ disease\ onset^{CAG}\ (parent)] \end{aligned} \quad (1)$$

For example, the estimated time to onset in a given index participant is increased if his or her parents' actual disease onset was later than estimated from the CAG repeat number. The differences of both prediction models in relationship to the SARA score are shown in Figure 1. The actual disease of onset in the parents was determined by the participants' self-report of first onset of gait difficulty during their examination by a neurologist, as done previously.[28]

Analyzing Posture and Gait Tasks With Increasing Complexity

To unravel the first preclinical changes in SCAs, we employed a battery of coordinatively demanding stance

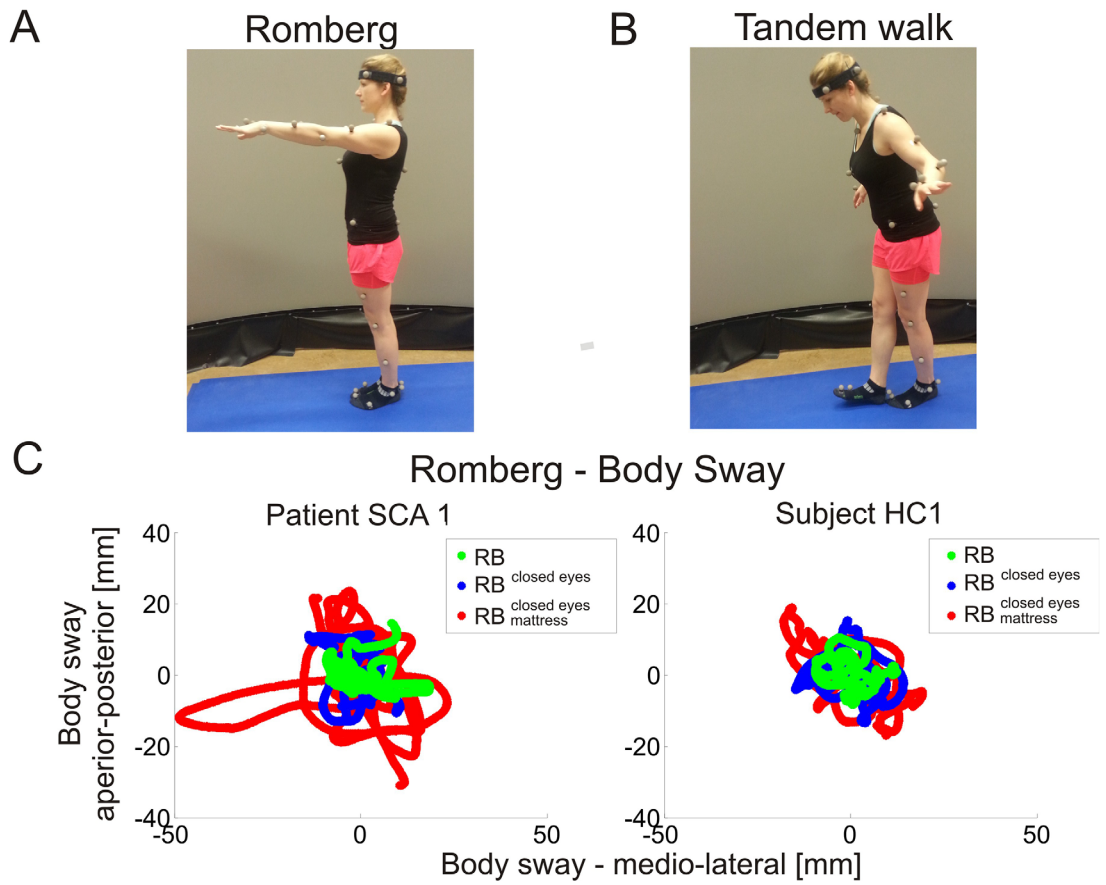

FIG. 2. Snapshots of a healthy participant performing the Romberg test (**A**) and tandem walk (**B**) on a 3-cm thick mattress. (C) Illustration of the body sway determined by the path of the cog (centre of gravity) for the different Romberg conditions. Both an exemplary spinocerebellar ataxia (SCA) patient from the group with patients with SCA 1, 2, 3, or 6 in the early clinical stage of the disease with a SARA score of 3-8 ($SCA^{SARA3\text{-}8}$) and a healthy participant show an increased body sway in the conditions with closed eyes and in particular with closed eyes on a mattress, yet increases are larger in the patient.

and gait tasks, predicting that motor abnormalities might unravel in particular with increasing motor demands. According to this strategy, we started with movement tasks identical to those used in clinical tests, followed by tasks with gradually increasing balance requirements and motor complexity.

We examined the following different stance conditions of increasing motor demand: standing still for 30 seconds with feet closed in the Romberg position and (i) eyes open (RB), (ii) eyes closed ($RB^{closed\ eyes}$), (iii) eyes closed on a mattress ($RB^{closed\,eyes}_{mattress}$; Fig. 2A). In addition, we examined different walking conditions of increasing motor demand: straight walking, tandem walking, and tandem walking on a mattress (Fig. 2B). Participants walked on a 10-m long walkway, whereby the capture volume contained only the 7 meters in the center of the walkway to exclude step cycles during acceleration and deceleration phases. From each participant, we analyzed 15 to 20 step cycles within 5 trials at a self-determined pace. In tandem walking, the participants were instructed to walk on an imagined straight line, placing 1 foot directly after the other (heel to toe). We recorded 20 to 25 step cycles within 3 trials from each participant.

Motor performance was quantitatively assessed using a VICON (Oxford Metrics, Oxford, UK) motion capture system with 10 cameras. The 3-dimensional movement trajectories were recorded at a sampling rate of 120 Hz using 41 reflecting markers. The trajectories were preprocessed using commercial software provided by VICON, which fits a kinematic model to the marker trajectories and extracts velocities, joint angles, and the course of the center of mass. For stance analyses, body sway was determined by measuring the path length of the center of gravity (projection of the center of mass on the floor; Fig. 2C). For gait analyses, we focused on spatiotemporal variability measures of step length and step cycle time, which have been shown to be most sensitive to characterize ataxic gait[14-16] and to detect subclinical gait changes.[13,19] Variability measures were calculated using the coefficient of variation = σ/μ, normalizing the standard deviation with the mean value.[32] In addition, we analyzed gait speed and gait asymmetry to show that they had no influence on gait variability (Supplement 1).

Statistics

Group differences (HC, nMC, $MC^{SARAp\&g=0}$, $MC^{SARA<3}$, and $SCA^{SARA3\text{-}8}$) on movement features were

determined by the nonparametric Kruskal–Wallis test. When the Kruskal–Wallis test yielded a significant effect ($P < .05$), post-hoc analysis was performed using a Mann–Whitney U test for comparisons between groups. We report 2 significance levels: uncorrected ($P < .05$) and Bonferroni corrected for multiple comparisons (Romberg conditions $P < .05/3$; tandem $P < .05/4$). Differences in multivariate analysis combining different movement features and age were determined using multivariate logistic regression models[33] for nMC and $MC^{SARAp\&g=0}$. To generate and validate the logistic regression models, we used a 3-step procedure. First, models were established to discriminate between nonmutation carriers and mutation carriers using the feature sets from the $MC^{SARA<3}$ (here excluding subgroup $MC^{SARAp\&g=0}$) and $SCA^{SARA3\text{-}8}$ groups as prototypes for mutation carriers, and from HCs (here excluding subgroup nMC) as prototypes for the nonmutation carriers. Second, in the test step we determined model outputs as the degree of ataxic movement characteristics for the 2 critical groups, namely, $MC^{SARAp\&g=0}$ and nMC (for graphical overview, see Supplement 5). Third, we analyzed the generated outputs of groups nMC and $MC^{SARAp\&g=0}$ with respect to (a) group differences and (b) categorization capabilities by using them as input into a receiver operating characteristic (ROC) analysis[34] to determine the accuracy of the identification of preclinical mutation carriers $MC^{SARAp\&g=0}$ on a single-participant level.

For this multivariate analysis, we selected those features as candidates for logistic regression that showed a significant group difference in the Romberg test and tandem walking. The factor age was included into the logistic regression analysis to control for a possible influence of age. Using these features, we examined all 10 permutations of features sets comprising the 3 features. The Bonferroni-corrected significance level for the multivariate analysis is set to $P < .05/10$ (10 is the number of analyzed feature sets).

Spearman's rho was used to examine the correlation between movement features and the SARA scores as well as estimates of time-to-disease onset. Statistical analysis was performed using MATLAB (The MathWorks Inc., Natick, MA, US) and SPSS (IBM Corp., Armonk, NY,US).

Results

Changes in Posture and Gait Control in the Preclinical Stage

Differences in body sway were identified in all 3 stance conditions (Kruskal–Wallis tests: $\chi^2 > 30.1$, $P < .0013$); post-hoc analysis showed an increased body sway in both $MC^{SARA<3}$ and $SCA^{SARA3\text{-}8}$ versus HC ($P < .004$, Bonferroni-corrected for multiple comparisons; Fig. 3A).

For straight walking (Kruskal–Wallis tests $\chi^2 > 5.195$, $P < .07446$), $SCA^{SARA3\text{-}8}$ showed an increased step length variability when compared with $MC^{SARA<3}$ ($P = .02$) and HC ($P = .01$), but no significant differences were observed between $MC^{SARA<3}$ and HC ($P = .25$). In contrast, for Tandem and $Tandem_{mattress}$ (Kruskal–Wallis tests $\chi^2 > 22.1$, $P < .01$), $MC^{SARA<3}$ showed significant increased variability in step length and in step cycle time when compared with HC ($P < .006$, Bonferroni-corrected for multiple comparisons; Fig. 3B).

Motor Changes Are Already Present in Preclinical Participants Without Clinical Signs of Gait and Posture Disturbances

To investigate subtle movement changes in preclinical participants until completely without any clinical signs of gait and posture disturbances ($SARA_{posture\&gait} = 0$), we compared motor performance between $MC^{SARAp\&g=0}$ and nMC. There was a difference between $MC^{SARAp\&g=0}$ and nMC for the most challenging stance condition $RB_{mattress}^{closed\,eyes}$ ($P < .001$, Bonferroni-corrected for multiple comparisons; see Fig. 3A). For gait, differences were observed in Tandem (step length variability, $P = .01$; step cycle time variability, $P = .02$) and $Tandem_{mattress}$ (step cycle time variability, $P = .02$).

To further explore the discrimination between $MC^{SARAp\&g=0}$ and nMC, we performed a multivariate analysis (see the Methods section and Supplement 5). We selected features as candidates for logistic regression that showed a significant difference in stance and gait tasks. The factor "age" was included to control for its possible influence.

Logistic regression analysis revealed differences in model output (interpreted as degree of ataxic movement characteristics) for the following set of 3 features: age, body sway in $RB_{mattress}^{closed\,eyes}$, variability in step cycle time for Tandem. Degrees of ataxic movement characteristics differed between HC and $MC^{SARA<3}$ ($P = .0001$) and between nMC and $MC^{SARAp\&g=0}$ ($P = .0006$; Fig. 3 C).

Classification of Preclinical Patients

To examine whether the identified feature set is capable to discriminate $MC^{SARAp\&g=0}$ participants from nMC participants on a single-subject level, we computed a ROC analysis based on the outputs of the regression model (model output ≡ degree of ataxic movement characteristics). This ROC analysis revealed that for a threshold of 0.127, our model allowed a classification of individual $MC^{SARAp\&g=0}$ participants as mutation carriers with 100% sensitivity and 87.5% specificity (accuracy 93.8%; Fig. 3C). A single-subject analysis showed that only the 2 $MC^{SARAp\&g=0}$ participants with an estimated disease onset of more than 10 years showed a smaller model output than 1 of the nMC participants.

Motor Features Reflecting Progression Within the Preclinical Phase

We finally aimed to determine whether motor features help capture progression within the preclinical phase.

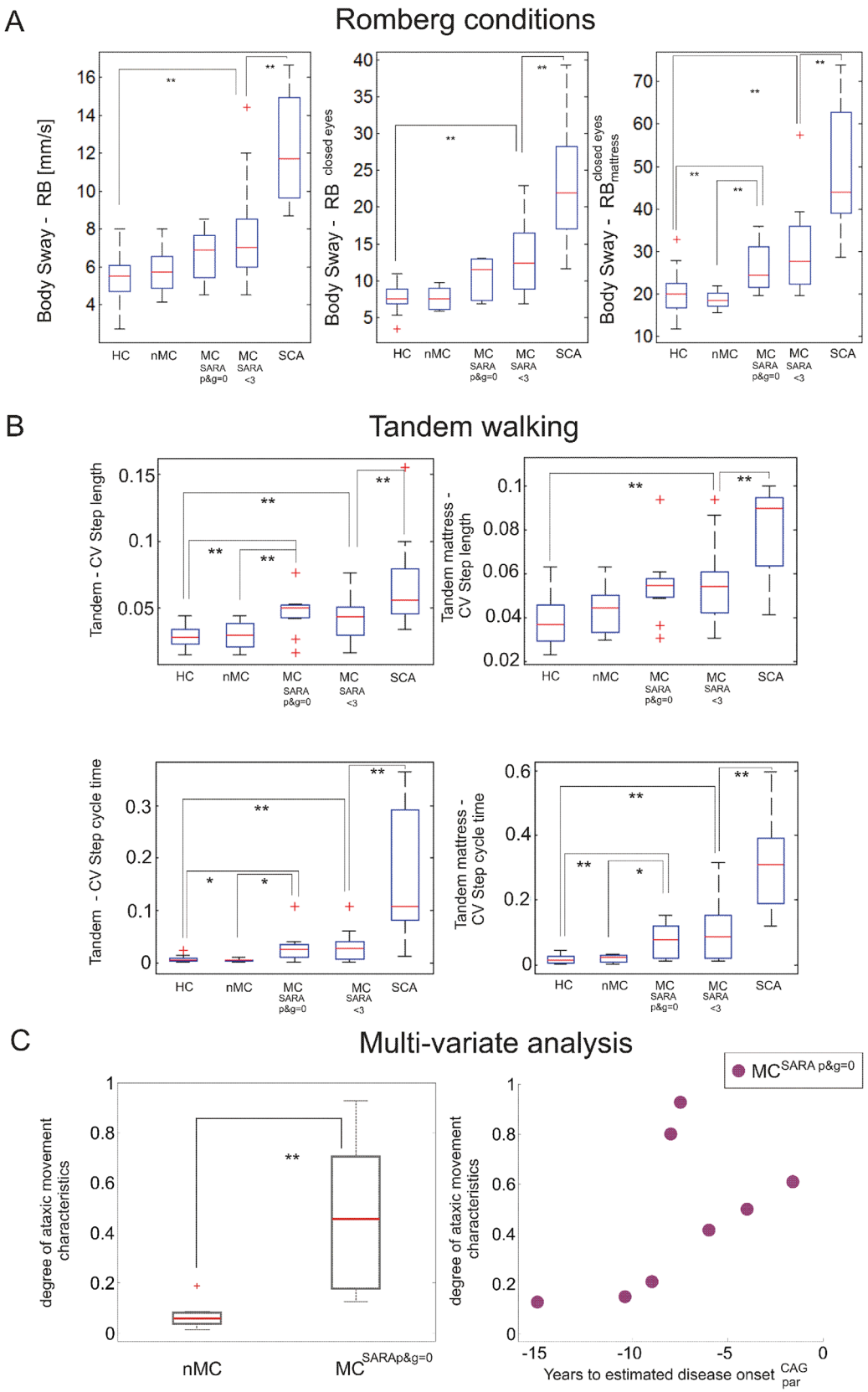

FIG. 3. Group results from quantitative movement analysis for the different Romberg stance conditions (**A**) and tandem walking conditions (**B**). Stars indicate significant differences between groups (*P <.05, **Bonferroni-corrected significance levels, see the Methods section). Group descriptions: HC, healthy controls; nMC, healthy subgroup of blood-related nonmutation carriers; $MC^{SARAp\&g=0}$, preclinical mutation carriers without clinical signs in posture and gait; $MC^{SARA<3}$, preclinical mutation carriers with SARA score <3; SCA, spinocerebellar ataxia patients with SARA 3-8; CV, coefficient of variation (see the Methods section). (**C**) Left panel: Results from the output of the logistic regression model for the feature set (age, body sway in $RB^{closed\ eyes}_{mattress}$, variability in step cycle time for tandem walk). The model output interpreted as degree of ataxic movement characteristics differed significantly between the subgroup of healthy, age-matched controls consisting of first-degree relatives of SCA patients tested negative for the mutation (nMC) and the subgroup of the preclinical mutation carrier group, all with a $SARA_{posture\&gait}$ subscore = 0 and SARA total score of ≤ 1 ($MC^{SARAp\&g=0}$; P =.006). Right panel: Analyzing model outputs in relation to the estimated duration-to-disease onset revealed that all mutation carriers with an estimated duration-to-disease onset < 10 years show a model output greater than all nMC participants. Only the 2 mutation carriers with a duration-to-disease onset > 10 years reduce the specificity of the categorization. [Color figure can be viewed at wileyonlinelibrary.com]

To this end, we examined the correlations between movement features and estimated time to disease onset in $MC^{SARA<3}$. Step length variability in $Tandem_{mattress}$ was associated with estimated disease onset for both models (unadjusted model $P = .036$; adjusted model $P = .0068$; Fig. 4). Also, body sway in $RB^{closed\,eyes}_{mattress}$ correlated with estimated disease onset ($P = .026$) and was observed only with the adjusted model. Overall, increases in step length variability and in body sway, respectively, with proximity to estimated disease onset were steeper in complex motor tasks (eg, mattress) than in simple motor tasks (Fig. 4). For diagrams of step cycle timing variability, see Supplement 2.

Discussion

The effectiveness of future interventions in the earliest stages of SCA will depend on the identification of biomarkers measuring preclinical disease progression in mutation carriers. The quantification of motor deficits as early as possible is crucial because motor symptoms are the key features across SCAs. In addition, such assessments will lead to a more detailed understanding of the earliest dysfunctions starting the evolution of ataxia. Although earlier studies have been restricted mostly to clinical scores such as the SARA[8] and International Co-operative Ataxia Rating Scale (ICARS)[35] or on qualitative descriptions of motor tasks,[6,36] quantitative studies are scarce.[18,37,38] Here we show that movement features help identify changes in preclinical SCAs when clinical signs are still completely absent, and even on a single-subject level.

Preclinical SCA Affects Both Posture and Gait Control, Particularly in Complex Motor Tasks

Body sway in the Romberg conditions and spatiotemporal variability in Tandem differentiated between preclinical patients ($MC^{SARA<3}$) and HCs. In contrast, no increased gait variability was observed in the preclinical patients for straight walking. These results contrast a finding of an earlier study on 6 preclinical SCA patients[18] that used, however, a different ataxia score ICARS [35] and cutoff value (ICARS cutoff value = 7 vs SARA cutoff value = 3). In fact, several of the preclinical patients in the previous study already showed first ataxia signs of ICARS gait items.[18]

Our finding of increased gait variability in preclinical patients not in normal walking, but in more complex gait conditions, is in line with previous studies with other neurodegenerative diseases. Studies in preclinical Parkinson's disease[39] and Fragile X-associated tremor-ataxia syndrome[40,41] observed increased gait variability only for more complex walking conditions.

Subclinical Motor Changes Are Detectable Before Their Clinical Manifestation

Although SARA<3 is commonly defined as a preclinical phase,[4,5,8] mutation carriers presenting with a SARA score of 2 or 2.5 can already show the first distinct clinical signs of ataxia. Correspondingly, $MC^{SARA<3}$ revealed a difference in the SARA score when compared with HCs ($P = .002$), confirming the results of a larger multicenter SCA study.[4] Thus, the advantage of motor measures would be particularly convincing if they helped identify ataxia-related movement changes even in those patients where no clinical signs of ataxia were seen, and where clinical scores do not show differences to HCs. This is the case for the $MC^{SARAp\&g=0}$ group, who showed no difference in SARA ($P = .97$) and the Inventory of Non-Ataxia Signs ($P = .5$) compared with nMC. In contrast to these two clinical scores, movement analysis indeed helped unravel changes for complex gait and posture conditions $MC^{SARAp\&g=0}$ when compared with nMC.

This difference is remarkable because nMC consisted exclusively of blood-related nonmutation carriers who were not aware of their carrier status, thus serving as an ideal blinded control group controlling for unspecific factors that might be present in members of SCA families (eg, subjective uncertainty under close motor assessment scrutiny). Interestingly, the SARA score of the nMC participants was on average as high as that of $MC^{SARAp\&g=0}$ patients (Table 1). This observation confirms the low specificity at the lower end of the SARA score.[9] Indeed, it was shown that about 20% of the HCs had positive ratings in at least 1 SARA item, predominantly related to kinetic functions of the nondominant hand.[8] Thus, movement analysis can refine the clinical assessments performed in earlier studies on preclinical SCA.[4,6] Specifically, the higher sensitivity might help detect preclinical motor changes much earlier than clinical measures. The estimated time to onset for the $MC^{SARAp\&g=0}$ is 7.6 years on average. In contrast, clinical assessments by the visual detection of missteps identified abnormalities in tandem gait about 1.2 years before disease onset, as shown in a longitudinal study of SCA2.[6]

Movement-Based Classification of Mutation Carriers

Although discrimination of mutation carriers and nonmutation carriers on a group level are informative, even more meaningful would be measures that help identify an affected patient on a single-subject level. Indeed, our feature set including features from 2 complex motor tasks and age helped discriminate $MC^{SARAp\&g=0}$ patients from nMC participants on a single-subject level with 100% accuracy for a range up to 10 years before estimated disease onset. Such a measure will be particularly valuable to classify

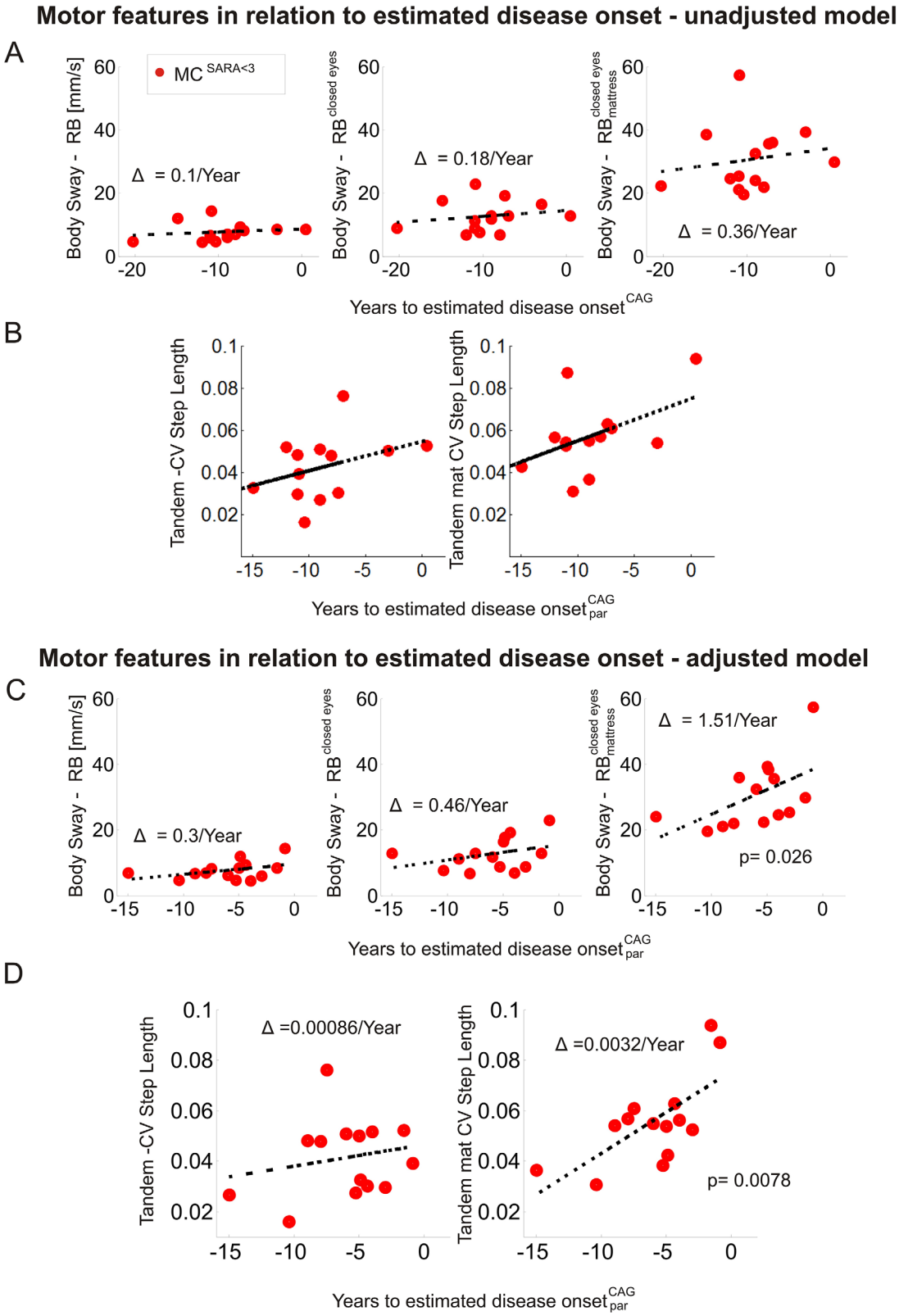

FIG. 4. Relationship between estimated time to disease onset and motor features for the preclinical mutation carriers with a scale for the assessment and rating of ataxia (SARA) score<3 ($MC^{SARA<3}$). Shown are relationships for estimates of onset according to the unadjusted model[28] (**A,B**) and according to the adjusted model (**C,D**). Each circle represents 1 participant. (**A**+**C**) Relationships between estimated time to onset and body sway in the different Romberg (RB) conditions. (**B**+**D**) Relationship between estimated time to onset and step length variability in tandem gait conditions with and without mattress. The black lines represent a linear fit of the data; the average changes per year are indicated by Δ. A steeper increase of change can be seen in the most complex stance and gait tasks, respectively, namely $RB^{closed\ eyes}_{mattress}$ and tandem gait on a mattress. *P* values indicate significant correlations between durations to estimated disease onset and movement parameters. [Color figure can be viewed at wileyonlinelibrary.com]

preclinical SCA patients in the future given that, in particular, intervention studies in preclinical patients of this rare disease will likely depend on a small patient series.

The selection of the factor age in the feature set with the highest discrimination capabilities indicates the importance to control for this factor in preclinical SCA studies. Subclinical movement changes are susceptible to aging, as shown for tasks such as the Romberg test and tandem walking.[25,26] Such an age effect was confirmed by our observation of a correlation between age and body sway in the Romberg test for HCs ($P = .0031$). This emphasizes the need to carefully select age-matched control groups and for age-dependent interpretations of subtle movement changes in challenging motor tasks.

Quantifying the Preclinical Course of SCA

Our study provides a fine-grained analysis on quantifying the progression of preclinical motor changes. Body sway in different Romberg conditions and spatiotemporal variability in tandem correlated with estimated time to onset, indicating a gradual increase of motor changes with increasing proximity to disease onset. $\text{Tandem}_{\text{mattress}}$ showed the fastest progression during the preclinical phase (Fig. 4), indicating that in particular complex motor tasks might be suitable to capture early motor changes.

An Adjusted Estimate of the Predicted Time to Onset

In general, correlations between movement changes and estimated time to onsets have to be interpreted with caution because estimations of time to onset are based on CAG repeat prediction models, which explain only 60% of the age-of-onset variance.[29] Specifically, the current unadjusted SCA prediction model does not take into account familial factors contributing to the individual's age of onset. Our adjusted model includes these factors. We observed the largest adjustment effects for patients with a SARA score of 2 to 2.5. Although already close to the threshold of SARA = 3, these patients would still be up to 10 years before their estimated onset according to the unadjusted model[28] (Fig. 1). This estimate thus seems implausible given the natural progression of 0.8 to 2.1 SARA points per year in the SCAs studied here.[42] In summary, our adjusted model leads to a closer capture of the SARA scores to estimated time to disease onset and to more plausible averages of times to onset for $\text{MC}^{\text{SARAp\&g=0}}$ and $\text{MC}^{\text{SARA<3}}$ (Table 1). Prospective cohort studies of larger preclinical SCA populations are certainly warranted to further validate this adjusted formula.

Limitations

This study has some limitations. Given the small sample size we cannot exclude the possibility that nonsignificant findings might be because of a lack of power. For example, step length variability in tandem walking on a mattress is marginally not significant ($P = .09$) in the distinction between $\text{MC}^{\text{SARAp\&g=0}}$ and nMC, although the same parameter is significant for tandem on the ground (Fig. 3B). This seems to be in particular relevant for more complex motor tasks, which can also show increased variability in HCs. On the other hand, if significant results are observed even in such small groups, this indicates that these effects are robustly present in the cohort. Another limitation of our study is its cross-sectional nature. However, the current data serve as a baseline for an ongoing prospective longitudinal study. Here we also investigate the preclinical course for specific SCA subtypes. In the current study, patients shared the same mutational SCA mechanism (CAG repeat expansion), but differed in their genotype (SCA 1, 2, 3, 6), thus representing clinically and biologically distinct SCA types, which are characterized by heterogeneous patterns of disease progression and distinct determinants on motor deterioration.[42] Our current study, however, was primarily designed to investigate early changes in posture and gait *across* specific SCA types, allowing one to find SCA general markers of early motor changes in the preclinical phase across SCAs.

Conclusions

The results of this study provide evidence for (1) quantitative measures of preclinical motor changes in SCA across specific types, which allow (2) to discriminate patients even on a single-subject basis in complex motor tasks and (3) that enable the quantification of disease progression in the preclinical phase. Thus, this study provides the basis for future observational studies investigating the characteristics and evolution of the preclinical phase of SCAs and also for both pharmaceutical and rehabilitative intervention trials. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's website