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Author(s):
Kanzler, Christoph; Lessard, Isabelle; Gassert, Roger; Brais, Bernard; Gagnon, Cynthia; Lambercy, Olivier

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Digital health metrics reveal upper limb impairment profiles in ARSACS

Christoph M. Kanzler a,b,*, Isabelle Lessard c, Roger Gassert a,b, Bernard Brais d, Cynthia Gagnon e,f, Olivier Lambercy a,b,1

a Rehabilitation Engineering Laboratory, Institute of Robotics and Intelligent Systems, Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland
b Future Health Technologies, Singapore-ETH Centre, Campus for Research Excellence And Technological Enterprise (CREATE), Singapore
c Groupe de recherche interdisciplinaire sur les maladies neuromusculaires (GRIMM), Centre intégré universitaire de santé et de services sociaux du Saguenay-Lac-St-Jean, Quebec, Canada
d The Montreal Neurological Institute and Hospital, McGill University, Quebec, Canada
e Faculty of Medicine and Health Sciences, Université de Sherbrooke, Quebec, Canada

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ABSTRACT

Objective: Adults with autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) often present with reduced upper limb coordination affecting their independence in daily life. Previous studies in ARSACS identified reduced performance in clinical assessments requiring fine and gross dexterity as well as prehension. However, the kinematic and kinetic aspects underlying reduced upper limb coordination in ARSACS have not been systematically investigated yet. In this work, we aimed to provide a detailed characterization of alterations in upper limb movement patterns and hand grip forces in 57 participants with ARSACS.

Methods: We relied on a goal-directed technology-aided assessment task, which provides eight previously validated digital health metrics describing movement efficiency, smoothness, speed, and grip force control.

Results: First, we observed that 98.3% of the participants were impaired in at least one of the metrics, that all metrics are significantly impaired on a population level, and that grip force control during precise manipulations is most commonly and strongly impaired. Second, we identified high inter-participant variability in the kinematic and kinetic impairment profiles, thereby capturing different clinical profiles subjectively observed in this population. Lastly, abnormal goal-directed task performance in ARSACS could be best explained by reduced movement speed, efficiency, and especially force control during precise manipulations, while abnormal movement smoothness did not have a significant effect.

Interpretation: This work helped to refine the clinical profile of ARSACS and highlights the need for characterizing individual kinematic and kinetic impairment profiles in clinical trials in ARSACS.

1. Introduction

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a neurodegenerative genetic disorder caused by a mutation in the SACS gene, which was described initially from the Quebec province in Canada and is by now the second most common recessive ataxia worldwide [1,2]. ARSACS can have an impact on the pyramidal, cerebellar, and neuropathic systems, thereby leading to a variety of clinical phenotypes with differently pronounced impairments [3].

A common impairment in ARSACS is abnormal upper limb coordination [2], which has typically been studied using conventional clinical assessments, such as the Nine Hole Peg Test (NHPT) or the Standardized Finger-Nose Test (SFNT) [3–5]. This revealed that persons with ARSACS have, for example, abnormal gross and manual dexterity, which can stem from the ataxic features of the disease as well as reduced prehension resulting from distal neuropathy. However, the reliability of the NHPT in ARSACS has been deemed as insufficient, thus limiting its interpretability and relevance [6]. Even more importantly, both the NHPT and SFNT provide a single time-based outcome measure, thereby leaving it unclear which aspects of upper limb sensorimotor control, such as movement efficiency, speed, or grip force control, are most affected and how they vary across individuals.

Technology-aided assessments bring the opportunity to study those fine aspects of upper limb coordination by providing kinematic and...
kinetic data collected during well-controlled goal-directed tasks [7,8]. Recently, a first technology-aided assessment, the Virtual Peg Insertion Test (VPIT), and eight of its digital health metrics capturing movement patterns and hand grip forces during a goal-directed task have been identified as valid and reliable in the adult ARSACS population [9,10]. However, it remains to be shown whether such digital health metrics can provide novel insights on the nature and mechanisms of impaired upper limb coordination in persons with ARSACS.

The objective of this study is to characterize the kinematic and kinetic aspects of upper limb coordination in persons with ARSACS on an individual and population-level based on normative reference values. Further, the secondary objective is to describe inter-participant variability in kinematic and kinetic behavior and the influence of abnormal kinematics and kinetics may have on the time to complete a goal-directed task. We hypothesized that kinematic and kinetic aspects of upper limb coordination are frequently impaired in persons with ARSACS, that participants have differentially pronounced kinematic and kinetic impairment profiles, and that abnormal kinematics and kinetics increase the time to perform a goal-directed task.

2. Methods

2.1. Study design

Cross-sectional observational study. Part of the data presented herein were used in a previous analysis focusing on concurrent validity of the digital health metrics of the VPIT [10].

2.2. Participants and procedures

Participants were recruited from the registry of the neuromuscular clinic (n = 168) of the Centre Intégré Universitaire de Santé et de Services Sociaux (CIUSSS) du Saguenay–Lac-St-Jean (Québec, Canada), under ethical approval from the institutional review board of CIUSSS (ID MP-04-2016-166). Participants were included if they were at least 16 years old, had a genetically confirmed ARSACS diagnosis, and were able to provide informed consent. A stratified random sampling based on age (16–29, 30–39, 40–49, and 50–59y) and sex (men and women) was applied to recruit a representative population of participants. Exclusion criteria were concomitant diseases affecting upper limb function, the use of a baclofen intrathecal pump, or a confirmed pregnancy. For all participants, written informed consent was collected before starting any study-related procedures.

After obtaining basic participant characteristics, such as age and sex, the VPIT protocol was performed to study fine aspects of upper limb coordination. In addition, conventional assessments were administered to provide a clinical description of upper limb sensorimotor function.

2.3. Virtual Peg Insertion Test (VPIT)

The VPIT is a technology-aided assessment featuring a goal-directed pick-and-place task that requires arm and hand function and was validated in various neurological populations [11–13]. In more details, the approach relies on a CE-certified haptic end-effector (Phantom Omni or Touch, 3D Systems, US), a custom-made grip force sensing handle with piezoelectric sensors (CentroNewton, PEWATRON, CH), and a personal computer with a virtual reality environment. This setup haptically renders a virtual manipulation task requiring the transport of nine virtual pegs into nine corresponding virtual holes as fast and as accurately as possible. A peg can be picked up by correctly aligning the virtual cursor, controlled by the haptic end-effector, and applying a grip force of at least 2 N. This level of grip force needs to be maintained until the hole is reached and the peg dropped therein. At the beginning of the assessment, participants are seated in a standardized position with approximately 90° elbow flexion, 45° shoulder abduction, and 10° shoulder flexion. In the current study, we applied a recently validated VPIT protocol consisting of an initial familiarization period and three task repetitions, which has higher clinical feasibility than the initially proposed protocol with five task repetitions [10].

The VPIT allows to gather end-effector position and grip force data at a sampling rate of 1 kHz. Through a processing framework that has been described in details in previous work [12,13], these data are transformed into a set of digital health metrics. In brief, the processing framework contains a low-pass filtering and interpolation operation followed by a temporal segmentation of the data into the transport (gross movement from peg pickup until peg insertion), return (gross movement from peg insertion until next peg pickup), peg approach (fine movement before peg pickup), and hole approach (fine movement before peg insertion) phases. These phases engage different aspects of upper limb motor control that can be quantified through appropriately chosen digital health metrics.

Recently, eight physiologically motivated core metrics were selected in a data-driven manner [13] and validated in persons with ARSACS with the adapted VPIT protocol with three repetitions [10]. These metrics have excellent clinimetric properties, in terms of test-retest reliability, absence of learning effects, and concurrent validity, for usage in cross-sectional studies in ARSACS. The definitions of the metrics and the aspects of upper limb coordination they capture are summarized in brief in the following. Smooth movements have been shown to be a hallmark of human motor control and are typically linked to a velocity profile with a characteristic bell shape [14]. In neurological disorders, this bell shape is known to degrade into a velocity profile with multiple submovements, thereby being an indicator of impaired motor control [15]. In the VPIT, movement smoothness is expressed through commonly applied metrics, two based on the minimum jerk principle (log jerk transport, log jerk return) and a frequency-based metric (spectral arc length (SPARC) return) [16,17]. Efficient goal-directed movements are typically assumed to be similar to a straight line between start and target, whereas persons with neurological disorders are often performing curved, inefficient movements [18]. Herein, movement efficiency is quantified by the path length ratio transport, which is defined as the ratio between the shortest possible distance and the actually covered distance. Further, the speed of goal-directed movements has systematically been shown to be one of the most affected parameter in persons with neurological disorders [7]. In the VPIT, movement speed is expressed through the maximum velocity metric during the return phase (velocity max return). Lastly, neurological disorders are known to affect precise hand grip force control [19]. Thus, the smoothness of grip force control was captured by a metric counting the number of peaks in the grip force rate profile (grip force rate num, peaks transport) and by analyzing the frequency content of the grip force rate profile (grip force rate SPARC transport, grip force rate SPARC hole approach).

Lastly, the metrics are normalized with respect to a previously established reference population of 120 able-bodied controls [13]. In more details, to enable an accurate comparison between groups without confounds, mixed effects models are used to correct for potentially influencing factors such as age, sex, and handedness. Subsequently, the metrics were expressed as a statistical distance to the median and variability of the reference population and further normalized with respect to the worst recorded task performance. Hence, this normalizes all metrics on a comparable scale (referred to as normalized VPIT scores) from]-∞, +∞[, where 0% indicates median reference performance and 100% indicates worst observed task performance.

2.4. Conventional clinical assessments

Conventional assessments were performed to enable a clinical description of the population. A convergent validity analysis comparing conventional clinical assessments and specific digital health metrics was already performed in previous work and was, thus, not considered herein anymore [10]. The available clinical assessments include the Disease Severity Index-ARSACS (DSI-ARSACS), which provides a
description of disease severity through eight items capturing upper and lower limb function, mobility, bladder function, and speech (best score: 0; worst score: 38) [4]. In addition, the Scale for the Assessment and Rating of Ataxia (SARA) was administered to describe gait quality, ability to stand and sit, speech disturbances, and lower and upper limb coordination, the latter based on a finger tracking test, a finger to nose test, and rapid alternating hand movements (best score: 0; worst score: 40) [20]. Further, the SFNT provides a measure of upper limb coordination, as it counts the number of alternating movements between nose and a target at 40 cm distance that can be achieved within 20 seconds [5]. Also, the NHPT, measuring the time to transport of nine physical pegs into nine physical holes, serves as a descriptor of fine manual dexterity [21]. Lastly, power grip and pinch grip strength was measured using a Jamar dynamometer and a pinch gauge (Baseline Pinch Gauge, Fabrication Enterprises Inc., Irvington, NY) [22].

2.5. Data analysis

Continuous variables were reported using median and interquartile range.

2.5.1. Analysis of kinematic and kinetic raw data

First, upper limb kinematics and kinetics were analyzed on a population level based on the available raw data collected by the VPIT. For this purpose, the time-series of a specific movement phase were interpolated to the same length and averaged within each participant. Subsequently, the average and standard deviation per population (ARSACS and able-bodied controls) was visualized and statistical parametric mapping was used to indicate statistically significant differences in the time-series [23]. Here, an age-matched control population was chosen by selecting all able-bodied controls within the age range of the persons with ARSACS. This was done to remove confounds of age, as the mixed effect model procedure can only be applied to the calculated VPIT metrics and not the raw data.

2.5.2. Analysis of digital health metrics on a population and individual level

Second, the processed digital health metrics, expressed as normalized VPIT scores, were visualized and statistically compared between the ARSACS and the able-bodied control population. Non-parametric Mann-Whitney-U tests were used to identify statistically significant differences between the groups. Also, the 95th-percentile of the able-bodied control population was used as a threshold to identify persons with ARSACS that exhibit abnormal task performance [13]. Further, individual kinematic and kinetic impairment profiles were analyzed by evaluating which digital health metrics indicate abnormal task performance for each person with ARSACS. To describe inter-participant variability for the different metrics, we calculated the coefficient of variation (in %) across participants for each metric, which is defined as the standard deviation across participants divided by the mean across participants. To understand how much variability in the VPIT metrics can be explained by clinical severity levels, we correlated the number of digital health metrics that indicate abnormal task performance with the SARA score, which is a measure of global disease severity including speech, upper and lower limb function, and walking. Further, to understand whether the VPIT metrics capture different and complementary aspect of movement patterns and hand grip force control, we calculated Spearman correlation coefficients between all VPIT metrics.

2.5.3. Analysis of kinematic and kinetic aspects influencing goal-directed task performance

Third, a linear regression analysis was performed to describe the kinematic and kinetic aspects that influence overall task performance in the VPIT. For this purpose, the VPIT task completion time (time from first peg pickup until last peg insertion) was used as a dependent variable and the eight kinematic and kinetic VPIT metrics were used as independent variables (details in supplementary materials (SM)).

All variables were entered as normalized VPIT scores, to avoid confounding effects such as age and sex. The model fit was evaluated using the adjusted coefficient of determination (\( R^2 \)) and an F-test comparing the fitted model with a constant model. For each independent variable, coefficient estimate and standard error, t-statistic, and p-value were calculated (significance level 0.05).

3. Results

Data from 57 persons with ARSACS that successfully completed the VPIT protocol was used for the analysis (age 35.0 ± 13.0 years, 47.4% men). Participant characteristics are reported in Table 1. Clinical assessments indicated mostly mild to moderate upper limb disability levels and all participants had abnormal manual dexterity as measured by the NHPT, relative to the 95th-percentile of publicly available age- and sex-matched normative values of the NHPT [21]. For the analysis of the VPIT metrics, publicly available normative values from a reference population of 120 able-bodied controls (age 51.1 ± 31.0 years, 50% men) were used [13]. These were age- and sex-stratified in 10-year brackets across the age range of 20–80 years. For the comparison of raw data between persons with ARSACS and able-bodied controls, an age-matched able-bodied subpopulation was used (n = 80, age 41.1 ± 20.3 years, 50% men).

Kinematic and kinetic time-series data averaged over all participants during different phases of the task can be found in Fig. 1. On a population level, statistically significant differences between persons with ARSACS and able-bodied controls could be observed across all movement phases.

The processed digital health metrics of the VPIT are visualized in Fig. 2. On a population level, persons with ARSACS showed statistically significantly worse task performance in all kinematic and kinetic aspect of upper limb coordination. In more details, the percentage of persons with ARSACS indicating abnormal behavior (i.e., worse than 95% of normative controls) in a VPIT metric was 70.2% for the grip force rate SPARC hole approach, 49.1% for the log jerk transport, 47.4% for the velocity max return, 35.1% for the grip force rate SPARC transport, 33.3% for the grip force rate peaks transport, 31.6% for the SPARC return, 28.1% for the log jerk return, and 24.6% for the path length ratio transport.

The kinematic and kinetic impairment profile of each participant is presented in Fig. 3. Out of 57 participants, 56 were impaired according to at least one VPIT metric. Further, 46 participants were impaired in at least two metrics, 35 participants in at least three metrics, 23 participants in an at least four metrics, 13 participants in at least five metrics, 1 participants in at least six metrics, and 1 participant in at least seven metrics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
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<tbody>
<tr>
<td>Participants with ARSACS</td>
<td>n = 57</td>
</tr>
<tr>
<td>Age (y)</td>
<td>35.0 ± 13.5 (16-61)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Men 27 (47.4) Women 30 (52.6)</td>
</tr>
<tr>
<td>Homozygous, n (%)</td>
<td>Yes 52 (92.9) No 47 (83.1)</td>
</tr>
<tr>
<td>Disease Severity Index-ARSACS (0–38)</td>
<td>15.3 ± 10.5 (4.5–35.5) n = 52</td>
</tr>
<tr>
<td>Scale for the Assessment and Rating of Ataxia (0–40)</td>
<td>19 ± 14 (4–36) n = 56</td>
</tr>
<tr>
<td>Standardized Finger-Nose Test (# of repetitions)</td>
<td>10.4 ± 4.0 (5.8-21.3) n = 56</td>
</tr>
<tr>
<td>Nine Hole Peg Test (s)</td>
<td>44.2 ± 23.5 (23.9-144.9) n = 56</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>29.2 ± 15.9 (17.2-59.1) n = 55</td>
</tr>
<tr>
<td>Pinch strength (kg)</td>
<td>5.7 ± 2.2 (3.3-10.3) n = 55</td>
</tr>
</tbody>
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six participants in at least six metrics, three participants in seven metrics, and no participant was impaired in all eight metrics. The coefficient of variation across participants was 116.1% for SPARC transport, 91.6% for velocity max return, 86.8% for grip force rate SPARC transport, 86.6% for grip force rate peaks transport, 82.6% for log jerk return, 82.4% for path length ratio transport, 82.6% for log jerk transport, and 60.5% for grip force rate SPARC hole approach. The correlation between the number of VPIT metrics that indicate abnormal task behavior and the SARA was $\rho = 0.29$, $p < 0.05$.

From the 28 calculated Spearman correlations between VPIT metrics, 11 showed statistical significance ($p < 0.05$, Table 2). Of those 11 correlations, four were moderate ($\rho = 0.54–0.66$), five were low ($|\rho| = 0.30–0.47$), and two were very low ($\rho = 0.25–0.29$). The moderate correlations were observed between log jerk transport and SPARC return, between velocity max. return and SPARC return, between force rate SPARC hole approach and path length ratio transport, and between force rate num. peaks transport and velocity max. return.

Lastly, the kinematic and kinetic underpinnings of reduced task performance, as measured by the task completion time, was evaluated using a linear regression model. The model was fitting the data adequately, with an adjusted $R^2$ coefficient of 0.64 ($F = 13.2$, $p < 0.001$), and assumptions for co-linearity, heteroscedasticity, and normality of residuals were fulfilled (details in Figure SM1 and Table SM1). The metrics that had a statistically significant influence on reduced task performance were the velocity max. Return (coefficient = 0.33, standard error = 0.08, $t = 4.0$, $p < 0.001$), the grip force rate SPARC hole approach (coefficient = 0.43, standard error = 0.07, $t = 6.4$, $p < 0.001$), and the path length ratio transport (coefficient = 0.69, standard error = 0.23, $t = 3.0$, $p < 0.01$).

4. Discussion

ARSACS is described as the second most common recessive ataxia in Europe and currently serves as a disease model for a large consortium of researchers working to advance clinical trial readiness in ataxic disorders [2,24]. This high attention in ARSACS paired with abnormal upper limb coordination being a cardinal sign in ataxic disorders create a strong interest in advancing the understanding of behavioral mechanisms of upper limb impairments [8].

This study permitted for the first time a comprehensive documentation of upper limb coordination in a representative ARSACS population (57 participants) based on digital health metrics, which allows to
refine our understanding of the clinical profile of persons with ARSACS. Our main findings were the following: First, 98.3% of persons with ARSACS were impaired in at least one kinematic and kinetic metric describing upper limb coordination and all metrics were significantly impaired on a population level. Second, we observed that persons with ARSACS have different kinematic and kinetic impairment profiles: while grip force control during fine manipulations was consistently impaired across most individuals, other metrics describing, for example, movement smoothness, were impaired only in selected individuals. Lastly, we found that abnormal goal-directed task performance in ARSACS, as measured by the VPIT task completion time, could be best explained by reduced movement speed, movement efficiency, and especially grip force control during precise manipulations, but not abnormal movement smoothness.

4.1. Impaired aspects of upper limb coordination

Previous studies in persons with ARSACS relied on conventional clinical outcome measures, such as the SFNT or the NHPT, to capture progressive decrease of proximal coordination and fine dexterity \cite{4,5}. In addition, Bui et al. performed a first kinematic evaluation in 13 participants with ARSACS based on an instrumented Archimedes spiral that needs to be traced with the fingertip on a tablet \cite{25}. While a frequency analysis allowed to accurately discriminate able-bodied participants and persons with ARSACS, this paradigm does not include gross goal-directed arm and hand movements and does not allow to study hand grip force control, thereby only describing selective aspects of upper limb coordination. This was also a limitation in studies performed in other ataxic disorders that relied on, for example, an instrumented

![Digital health metrics](image-url)

**Fig. 2.** ARSACS has consistently impaired upper limb movement patterns and grip force control. Digital health metrics describing movement and grip force profiles are visualized for the ARSACS (red) and an able-bodied reference population (gray). Metrics are normalized such that 0% indicates the median of the reference population, 100% the participant in the existing VPIT database with worst task performance, and negative values indicate superior task performance compared to the reference population. The red triangle indicates the 95th-percentile of the reference population, which is used as a cut-off to determine abnormal behavior according to a metric. **p < 0.001. TP: Transport. RT: Return. HA: Hole Approach. SPARC: Spectral Arc Length.

![Participant-specific impairment profiles](image-url)

**Fig. 3.** ARSACS has participant-specific kinematic and kinetic impairment profiles. The value of the digital health metrics were binarized based on the 95th-percentile of able-bodied controls (i.e., abnormal behavior cut-off) and visualized in black (abnormal behavior present) or white (abnormal behavior absent) for each participant. TP: Transport. RT: Return. HA: Hole Approach. SPARC: Spectral Arc Length.

<table>
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<th>Table 2</th>
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<tr>
<td>Spearman correlations between digital health metrics from the VPIT calculated for the ARSACS population. *indicates p &lt; 0.05. TP: Transport. RT: Return. HA: Hole Approach. SPARC: Spectral Arc Length.</td>
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<tr>
<td>---------------------------------------------------------------</td>
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<tr>
<td><strong>Log jerk</strong></td>
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<tr>
<td><strong>Log jerk TP</strong></td>
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<tr>
<td><strong>Log jerk RT</strong></td>
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<td><strong>Path length ratio TP</strong></td>
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<tr>
<td><strong>Path length ratio RT</strong></td>
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<tr>
<td><strong>Velocity max. RT</strong></td>
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<td><strong>Force rate nu. peaks TP</strong></td>
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<td><strong>Force rate SPARC TP</strong></td>
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<td><strong>Force rate SPARC HA</strong></td>
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finger-to-nose test or a computer mouse-based pointing task [8,26–29]. A previous pilot study with the VPIT showed its general feasibility in the ARSACS population [9].

In this work, we expand these observations by showing that kinematic and kinetic aspects underlying upper limb coordination, including efficiency, smoothness, speed, and grip force control, are frequently impaired in persons with ARSACS. Interestingly, the most common and strongest abnormalities (70.2% of all participants with ARSACS) were observed for the grip force rate SPARC hole approach metric, which captures the smoothness of grip force adaptations during fine manipulations and might be related to the neuropathic and spino-cerebellar impairments of the disease [30,31].

Also, the smooth adaptation of grip forces during gross movements was less frequently and less strongly impaired (grip force rate SPARC transport: 35.1% of population impaired; grip force rate num. peaks transport: 12.5% of population impaired) than during precise manipulations. This highlights that grip force control is especially a major challenge for persons with ARSACS when approaching a target and less during the ballistic part of a goal-directed movement. This might be because precise manipulations when inserting a peg rely on sensory feedback loops, whereas ballistic movements are controlled more in a feedforward manner [32]. This is congruent with the idea that the cerebellum is strongly involved in sensory feedback processing and that abnormal sensory processing, for example in the cerebellum, contributes to coordination when reaching for a target [33]. Thus, the observed emphasis of grip force impairments during precise manipulations could confirm the expected cerebellar involvement in ARSACS, which is added to neuropathic components affecting grip strength and grip force control [4,30].

Our findings about grip force control during dynamic, goal-directed movements in ARSACS complement the existing literature on cerebellar ataxias that focused on understanding predictive and reactive force control, force-load coupling, and response to perturbations [31,34,35].

4.2. Kinematic and kinetic impairment profiles

While the metric describing grip force control during fine manipulations indicated consistent impairment for most persons with ARSACS, heterogenous individual-specific impairment profiles emerged when looking at the remaining kinematic and kinetic metrics. Specifically, high inter-participant variability was observed for the metrics describing movement smoothness, speed, efficiency, and grip force control during ballistic movements. These observations provide insights beyond what can typically be gained from individual clinical scores. This is illustrated by the rather low correlation between SARA and number of VPIT metrics indicating abnormal task performance, thus highlighting the complementary value of the digital health metrics. Also, this suggests that most aspects of movement patterns and hand grip force control are not stereotyped in persons with ARSACS when performing a complex goal-directed manipulation task, such as the VPIT, and that they instead depend on the clinical profile of the individual. Specifically, we expect that these different kinematic and kinetic impairment profiles stem from a person-specific expression of pyramidal, cerebellar, and neuropathic ARSACS symptoms [4], thereby reflecting the high clinical heterogeneity of persons with ARSACS [2,4].

Further, the correlations between VPIT metrics indicate that the majority of VPIT metrics are not strongly correlated (Table 2) and capture different aspects of movement patterns and hand grip force control in persons with ARSACS. In addition, the covariance between metrics is sufficiently small to justify the inclusion of the metrics in linear regression models. While the two smoothness metrics calculated during the return (SPARC return and log jerk return) phase correlated moderately, it has been shown that these metrics have different technical properties and might be sensitive to different alterations of ballistic arm reaching movements [16,17]. A potential reason for the moderate correlation between SPARC return and velocity max. return metric might be that faster movements have less data samples, which influences the frequency spectrum of the data and, thus, the calculation of the SPARC metric. The moderate correlation between force rate num. peaks transport and velocity max. return might be because slower (i.e., longer) goal-directed movements have increased likelihood of having multiple peaks in the force rate profile. For the moderate correlation between force rate SPARC hole approach and path length ratio transport, it could be speculated that participants with a suboptimal movement path (i.e., low path length ratio) are also more likely to have a longer hole approach phase, which might affect the SPARC-based metric.

Overall, these results have implications for the design of future clinical trials: First, they highlight the need for personalizing and tailoring interventions to the individuals’ impairment profile with the promise of maximizing therapy outcomes. Second, they suggest that intervention-induced changes in ARSACS will likely act in a person-specific manner on individual aspects of motor control, thus requiring dedicated primary endpoints for subpopulations of patients. Third, while current pyramidal, cerebellar, and neuropathic ARSACS symptoms can already be captured using multiple dedicated clinical assessments, digital health metrics should be leveraged to comprehensively assess the influence of these symptoms on goal-directed upper limb movement patterns and hand grip forces. This promises to better understand the functional relevance of multiple ARSACS symptoms in the context of a single functional goal-directed task. Lastly, our results suggest that multiple kinematic and kinetic metrics are required to holistically describe impairment profiles in ARSACS, thereby justifying the application of complex assessment tools such as the VPIT.

4.3. Kinematic and kinetic aspects influencing task completion time

Clinical assessments commonly rely on the task completion time to describe a person’s ability to perform goal-directed tasks but are not able to explain underlying behavioral variability and capture the reasons for reduced task performance [21]. Herein, this issue was addressed using unique data from the VPIT, which allows modeling the task completion time of a goal-directed task based on the underlying behavioral variability, as defined by the kinematic and kinetic metrics of the VPIT. This revealed that significant contributors to reduced task performance in ARSACS are movement speed, efficiency, and especially grip force control during precise manipulations. Indeed, it is intuitive that suboptimal movement speed and efficiency have a direct influence on the task completion time. Similarly, impaired grip force control during precise manipulations having a strong influence on the task completion time is in line with the observation that grip force control was commonly and strongly impaired in a high proportion of persons with ARSACS, thereby underlining that this is a major issue in this population [3]. Interestingly, suboptimal movement smoothness was not significantly influencing the task completion time, potentially because this construct is sensitive to subtle jerky movements that do not affect overall task execution. Thus, even though movement smoothness is one of the most commonly quantified aspects of upper limb coordination in neurological disorders [7], it does not seem to influence performance in the functional task of the VPIT. Hence, personalized rehabilitation interventions in persons with ARSACS could therefore attempt to focus especially on improving movement speed, efficiency, and grip force control to advance functional task performance.

4.4. Limitations

Even though dysmetria is a common phenomenon in persons with ataxia, we did not directly quantify it in this work, for example through the position error when approaching a peg or hole, because the metric has been deemed as unreliable based on our previous work [13]. Nevertheless, dysmetria was still captured indirectly through the analysis, namely as part of the constructs of movement smoothness and movement efficiency. Also, a better understanding of the kinematic and
kinetic impairment profiles could have been achieved by describing sensory and motor impairments with neurophysiology which was not available for this study. Similarly, it would have been helpful to perform a subgroup analysis based on severity classification of neuropathic, pyramidal and ataxic signs, which is challenging to implement given the lack of methods for a clinically meaningful and comparable descriptions of each sign. Lastly, this study included mainly persons with ARSACS that were homozygous for the SACS gene, thereby not allowing to study the potential effect of this genetic factor on upper limb behaviors.

5. Conclusions

This study reveals that kinematic and kinetic aspects underlying upper limb coordination are frequently impared in persons with ARSACS, that grip force control during precise manipulations is most commonly and strongly impaired, and that this affects goal-directed task performance. Further, we identified large inter-individual variability in the kinematic and kinetic impairment profiles of persons with ARSACS, likely as a result of a person-specific expression of pyramidal, cerebellar, and neuropathic ARSACS symptoms. These novel insights helped to refine the clinical profile of ARSACS. In the future, the temporal evolution of kinematic and kinetic impairment profiles should be studied to better understand disease progression in ARSACS.

Declaration of Competing Interest

The authors state that they do not have any conflict of interest.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2023.120621.

References

[3] C. Gagnon, I. Lessard, C. Lavoie, et al., An exploratory natural history of ataxia of Charlevoix-Saguenay (ARSACS): expanding the genetic, clinical and neuropathic ARSACS symptoms. These novel insights helped to refine the clinical profile of ARSACS. In the future, the temporal evolution of kinematic and kinetic impairment profiles should be studied to better understand disease progression in ARSACS.

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Declaration of Competing Interest

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