

Reliability and validity of digital health metrics for assessing arm and hand sensorimotor impairments in persons with autosomal recessive spastic ataxia of Charlevoix-Saguenay

Christoph M. Kanzler (✉ christoph.kanzler@sec.ethz.ch)

<https://orcid.org/0000-0003-1214-8347>

Isabelle Lessard

Roger Gassert

Bernard Brais

Cynthia Gagnon

Olivier Lambercy

Research Article

Keywords: upper limb assessment, sensorimotor impairments, ARSACS, metrological properties, digital health metrics

Posted Date: October 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-987961/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is the second most frequent recessive ataxia and commonly features reduced upper limb coordination. Sensitive outcome measures of upper limb coordination are essential to track disease progression and the effect of interventions. However, available clinical assessments are insufficient to capture behavioral variability and detailed aspects of motor control. While digital health metrics extracted from technology-aided assessments promise more fine-grained outcome measures, these have not been validated in ARSACS. Thus, the aim was to document the metrological properties of metrics from a technology-aided assessment of arm and hand function in ARSACS, and ensure that those can be used as insightful endpoints. We relied on the Virtual Peg Insertion Test (VPIT) and used a previously established core set of 10 digital health metrics describing upper limb movement and grip force patterns during a pick-and-place task. We evaluated reliability, measurement error, and learning effects in 23 participants with ARSACS performing three repeated assessment sessions. In addition, we documented concurrent validity in 57 participants with ARSACS performing one session. Eight metrics had excellent test-retest reliability (intra-class-correlation-coefficient 0.89 ± 0.08), five low measurement error (smallest real difference 25.4 ± 5.7), and none strong learning effects (systematic change $\eta -0.11 \pm 2.5$). Significant correlations ($\rho 0.39 \pm 0.13$) with clinical scales describing gross and fine dexterity and lower limb coordination were observed. This establishes eight digital health metrics as valid and robust endpoints for cross-sectional studies and five metrics as potentially sensitive endpoints for longitudinal studies in ARSACS, thereby promising novel insights into upper limb sensorimotor control.

Introduction

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a genetic disorder with pyramidal, cerebellar and neuropathic impairments, all contributing to upper limb incoordination [1, 2]. ARSACS is the second most frequent recessive ataxia and currently serves as a disease model for a large international natural history study for recessive ataxias [1]. In order to personalize interventions to the specific impairment profile of an individual and to evaluate their effectiveness, sensitive and fine-grained outcome measures of upper limb coordination are of vital importance.

However, the clinically available outcome measures for upper limb coordination in persons with ARSACS are either based on a subjective and crude rating of movement quality or the time to complete functional tasks [3, 4]. Hence, such outcomes are not optimally suited to detect fine differences between individuals or to be sensitive to change in a clinical or research context. In addition, these assessments are not able to reveal the contribution of specific sensorimotor impairments, associated with the pyramidal, cerebellar, or neuropathic system, to abnormal performance in goal-directed tasks. Thus, in order to personalize interventions to the specific impairment profile of an individual and to evaluate their effectiveness, sensitive and fine-grained outcome measures are of vital importance.

Technology-aided assessments can record objective data about upper limb movement patterns and grip forces during goal-directed functional tasks [5, 6]. These traces are expected to reveal inter-individual differences in task performance that relate to the specific sensorimotor impairment profile of an individual. In addition, these traces can be transformed into digital health metrics, describing for example movement smoothness or efficiency. These can serve as complementary, objective quantitative outcomes that promise to be more sensitive to change, thereby potentially allowing for a reduction of required sample sizes for clinical trials [7]. Technology-aided assessments have been successfully validated and applied in stroke population [7–9], but only found little attention in recessive ataxias [10, 11]. Most importantly, before using digital health metrics as endpoints for clinical trials, it is essential to document the metrological properties for a specific target population [11, 12]. Also, the dependency of these metrological properties on the number of assessment task repetitions should be investigated, as rapidly applicable assessments are required to ensure their clinical implementation [13, 14].

One of such technology-aided assessments is the Virtual Peg Insertion Test (VPIT), which features a goal-directed pick-and-place task on a personal computer, relying on a haptic end-effector with a grip force-sensing handle [15]. The VPIT protocol consists of an initial familiarization period and five task repetition, which can typically be performed in about 16 minutes in persons with neurological injuries [16]. Previously, a core set of 10 digital health metrics describing movement patterns and grip force control was established and validated in able-bodied and stroke populations [11, 17]. Also, as part of a pilot project, the feasibility of the VPIT in ARSACS has been successfully established [10].

Building on this foundation, the aim of this study was to document the following metrological properties of the VPIT digital health metrics in the adult ARSACS population: 1) test-retest reliability and measurement error; 2) learning effects and; 3) concurrent validity. Furthermore, the secondary objective was to evaluate the test-retest reliability and measurement error of the metrics when considering only three instead of five task repetitions, thereby potentially further enhancing the clinical feasibility of the assessment. Based on our previous work with the VPIT in post-stroke individuals and related literature [5, 13, 17], we hypothesized that a subset of the VPIT core metrics is statistically robust in ARSACS and that a reduction from five to three task repetitions leads to an acceptable decrease in robustness of the metrics.

This project will permit to provide evidence about the validity and reliability of novel digital health metrics extracted from a technology-aided assessment in the ARSACS population, thereby promising novel insights into the mechanism of sensorimotor impairments in recessive ataxias.

Methods

Study design

Methodological study embedded in a longitudinal observational study.

Participants and procedures

Participant recruitment was done among 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). Inclusion criteria were (1) ≥ 16 years old, (2) genetically confirmed ARSACS diagnosis, and (3) ability to provide informed consent. A stratified random sampling strategy was used by age group (16–29, 30–39, 40–49, and 50–59y) and sex (men and women). Patients with other diseases causing functional limitations, having a baclofen, or being pregnant were excluded. The study was approved by the ethics review board of the *CIUSSS Saguenay–Lac-St-Jean* (ID MP-04-2016-166) and written informed consent was obtained from participants.

Participants performed the VPIT protocol and a battery of clinical assessments in a standardized order (Figure 1D), which was used to study concurrent validity (*validity dataset*). Furthermore, a subset of participants took part in the reliability study where the VPIT was administered again within a period of 3 weeks to study test-retest reliability (*reliability dataset*).

Technology-aided assessment: Virtual Peg Insertion Test (VPIT)

The VPIT (Figure 1A) is a technology-aided assessments for quantitatively assessing upper limb movement patterns and grip force control [15]. The approach consisting of a commercially available, CE-certified haptic end-effector (PhantomOmni or Touch, 3D Systems, US), a custom-made force sensing handle with piezoresistive sensors (CentoNewton, PEWATRON, CH), and a virtual reality environment displaying a goal-directed task on a personal computer. In more details, the task displays nine virtual pegs that need to be transported into nine virtual holes by coordinating arm movements and hand grip forces. Specifically, a peg can be picked up by first aligning a virtual cursor, controlled by the haptic end-effector, with the peg and then applying and maintaining a grip force of at least 2N. Subsequently, the peg can be transported towards the hole and inserted in it by reducing the grip force below 2N. Throughout the task, the virtual pegboard is haptically rendered by the end-effector device and a timer displays the elapsed time. Before performing the task, participants received standardized instructions and are seated in a standardized position with approximately 45° shoulder abduction, 10° shoulder flexion, and 90° elbow flexion. The standard VPIT protocol consists of an initial familiarization period, where participants can understand how to use the haptic end-effector, and subsequently five repetitions of the task that are used for post-processing.

This highly standardized setup allows to gather high quality data on end-effector position and hand grip forces at a sampling rate of 1kHz [15]. These data are fed into a previously established state of the art signal processing pipeline, allowing to extract 10 sensor-based core metrics describing movement smoothness, speed, accuracy, efficiency, and grip force control during different behavioral phases of the task [11]. These are defined as the *transport* phase (gross movement from peg pickup until insertion), the *return* phase (gross movement from peg insertion until next peg pickup), the *peg approach* phase (fine movement before picking up a peg), and the *hole approach* (fine movement before inserting a peg). A detailed pathophysiological motivation and mathematical definition of the 10 sensor-based metrics,

which were selected based on a data-driven statistical procedure from a set of 77 candidate metrics, is provided in previous work [11] and is briefly summarized in the following: Movement smoothness is typically expressed through bell-shaped velocity profiles of a goal-directed movement in able-bodied controls and deviations from the typical bell-shape are observed in neurological disorders [18, 19]. Herein, smoothness was characterized using the normalized logarithmic jerk metric calculated during transport and return (*log jerk transport/return*), as well as the spectral arc length metric calculated during return (*SPARC return*) [18, 19]. Movement efficiency is typically expressed through straight movements between start and target in able-bodied controls, whereas neurological subjects often perform uncoordinated movements with inefficient, curved trajectories and exhibit a spatial overshoot when approaching the target, which is a hallmark symptom in persons with cerebellar disorders [20–22]. In this work, we relied on the *path length ratio* (ratio of shortest possible distance divided by actually covered distance) calculated during *transport* and *return* to describe movement efficiency [20]. In addition, neurological disorders can affect movement speed, which was characterized using the maximum velocity during the *return* phase (*velocity max. return*). Also, potentially altered endpoint precision was described using a jerk-based metric calculated during the *peg approach* phase (*jerk peg approach*) [11]. Moreover, three metrics were defined to describe the smoothness of grip force coordination, namely the number of peaks in the grip force rate profile during the *transport* phase (*grip force rate num. peaks transport*) as well as the spectral arc length of the grip force rate profile during *transport* (*grip force rate SPARC transport*) and *hole approach* (*grip force rate SAPRC hole approach*). After the calculation of the metrics, the effect of demographic factors, such as age and gender, is removed through mixed effect models and the metrics are normalized with respect to a normative population of 120 able-bodied controls as well as previously recorded neurological subjects [11]. This provides a standardized representation of the metrics on an unbounded, continuous scale from $]-\infty, +\infty[$, where 0% corresponds to the median performance of the normative population, 100% to worst recorded task performance, and values below 0% to superior performance than the median of the normative population.

These core metrics were initially selected because of their excellent metrological properties in able-bodied controls and their ability to discriminative a normative reference population and a population of 89 persons with neurological disorders [11]. Further, we showed that the 10 core metrics are valid to describe sensorimotor impairments in stroke populations and that three metrics, namely the *log jerk transport*, *log jerk return*, and *force rate SPARC transport*, are expected to provide sensitive outcomes for monitoring physiological changes in longitudinal studies with stroke populations [17].

Clinical assessments

A battery of clinical assessments was performed to capture different sensorimotor impairments and activity limitations.

The severity of cerebellar ataxia symptoms was assessed using the SARA, which rates typical ataxic features including gait, upper limb deficits, and speech on a scale from 0 (no ataxia) to 40 (most severe ataxia) [3]. Power grip strength was measured using a Jamar dynamometer with a standardized procedure and three repetitions, with the average being used as the outcome measure [23]. Lateral pinch

strength between the thumb and index was measured using a pinch gauge and three repetitions (Baseline Pinch Gauge, Fabrication Enterprises Inc, Irvington, NY). Fine dexterity was assessed using the Nine Hole Peg Test (NHPT), which requires participants to insert and then to transport nine pegs in nine holes as quickly as possible [4]. The total time to complete the task is recorded in seconds and the average of two trials was used for analyses. Upper limb coordination was assessed using the standardized finger-nose test (SFNT) [24]. The SFNT requires participants to perform as many reaching movements as possible within 20 seconds, alternating between a 40cm distant target and the participants' nose. Lower limb motor coordination was assessed with the Lower Extremity Motor Coordination Test (LEMOCOT) [25]. Seated on a regular chair, participants alternately touched two targets placed 30 cm apart on the floor with their foot. One trial was performed for each side and the number of targets touched in 20 seconds was recorded. The LEMOCOT was found to be valid and reliable in the adult ARSACS population [25]. Functional independence in activities of daily living was measured using the Barthel Index for Activities of Daily Living (French version). Ten items were rated, for a maximum score of 100 representing total independence [26].

Data analysis

In order to characterize the metrological properties of the VPIT metrics, the COSMIN framework was used [12], and adapted for digital health metrics [11, 17]. Descriptive statistics were used for continuous variables (median, interquartile, ranges), and frequency and percentage for categorical variables.

To describe test-retest reliability, we calculated the intra-class correlation coefficient (ICC, version A,k) across all three measurement sessions. The ICC considers the intra- and inter-participant variability of a metric and describes its ability to discriminate multiple participants, with an $ICC > 0.7$ being defined as excellent test-retest reliability [27]. Moreover, we reported the smallest real difference (SRD) of a metric, which is the range of values where it is not possible to distinguish between measurement noise and an actual change in the measured construct, which is especially important for sensitively capturing longitudinal changes [28]. The SRD was calculated as $1.96 * \sqrt{2} * \sqrt{1 - ICC}$ and normalized with respect to the range of observed values, such that it can be compared across metrics, leading to the cut-off of $SRD\% \leq 30.3$ to identify metrics with relatively small measurement error [11]. To check for systematic bias in the metrics across assessment timepoints, a Bland-Altman analysis was performed [29]. Also, the normalized slope (η) across assessment timepoints was calculated to describe potential systematic learning effects, which might mask physiological changes observed in longitudinal studies. Strong learning effects were present if η was below -6.35% and statistically significant according to a paired t-test [11]. These analyses were performed on the *reliability* dataset, containing three repeated measurement sessions, each with five repetitions of the VPIT task. To further evaluate if the number of task repetitions could be reduced to enhance clinical feasibility, we repeated the described analysis when only considering the first three repetitions of the task at each timepoint.

For analyzing concurrent validity, we relied on the *validity* dataset, containing data from a single assessment session with three VPIT repetitions and performed a Spearman correlation analysis between digital health metrics and the clinical outcome measures. We defined a priori hypotheses about the

expected correlations based on the physiological motivation of the metrics and clinical scales, and previous studies in neurological disorders [5, 11, 17]. It is essential to mention that digital health metrics are expected to provide complementary information to the clinical scales, therefore typically leading to low to moderate correlations (e.g., correlation coefficients between 0.3 and 0.7) [5, 30]. In more details, we expected digital health metrics describing arm movement control to moderately correlate with clinical assessments involving arm movements, namely the Nine Hole Peg Test and the Standardized Finger-Nose Test. Similarly, we expected moderate correlations between digital health metrics describing the precise control of hand grip forces to clinical assessments requiring precise grip force control, namely the Nine Hole Peg Test. Further, we expected low correlations between the digital health metrics and clinical assessments of grip and pinch strength, as it is assumed that force control and strength are different, separable physiological systems [31, 32]. In addition, we expected low correlations with the LEMOCOT, as it is a measure of lower limb coordination, thereby being separated from upper limb coordination. Lastly, we expected a low correlation between the Barthel index and the digital health metrics, as the latter describes patterns of behavioral variability in a task-related setting that might not directly be related to independence of daily life.

Results

A total of 57 participants (mean age: 35.0 years, 47.4% were men) were recruited in the validity study (*validity* dataset, Figure 1, Table 1) and 23 participants (mean age: 35.0 years, 47.8% were men) were recruited in the test-retest reliability study (*reliability* dataset, Figure 1, Table 1).

Test-retest reliability, measurement error, and learning effects

The evaluation of test-retest reliability (ICC), measurement error (SRD%), and learning effects (η) can be found in Table 2. Across metrics, the ICC was 0.87 ± 0.11 (median \pm inter-quartile range), with only the *path length ratio return* (ICC 0.62) and the *jerk peg approach* (ICC 0.32) being below the cut-off of 0.7. The SRD% across metrics was 30.9 ± 18.7 , with the measurement error being below the cut-off of 30.3 for five metrics, namely *log jerk return* (27.5), *SPARC return* (25.4), *velocity max. return* (23.8), *grip force rate num. peaks transport* (28.9), and *grip force rate SPARC transport* (19.1). No strong learning effects were found between assessment timepoint one and two (η -1.3 ± 2.5) and between assessment timepoint two and three (η -0.1 ± 2.8). Even though a statistically significant learning effect was visible between timepoint two and three for the *velocity max. return* metric (η -5.07 , $p=0.019$, $t=-2.51$, $DoF=22$), the effect was not deemed as strong according to the cut-off (-6.35%).

When only considering three instead of five repetitions of the VPIT (Table SM1), across metrics, the ICC reduced by 0.04 ± 0.06 (min 0.01, max 0.30 for *jerk peg approach*), the SRD% increased by 1.72 ± 3.75 (min 0.05, max 32.27 for *jerk peg approach*), η between timepoint one and two increased by 0.02 ± 1.90 (min 0, max 6.28 for *log jerk return*), and η between timepoint two and three increased by 1.08 ± 5.84 (min 0, max 7.04 for *log jerk return*). When only considering three instead of five repetitions, the same eight metrics

were reliable, two additional metrics had insufficient measurement error (*log jerk return 31.3* and *grip force rate num. peaks transport 31.7*), and no metrics showed strong learning effects.

Table 1 Characteristics of the participants used for evaluating the reliability and validity of the VPIT metrics.

Characteristic	ARSACS validity dataset (n=57, 1 session)	ARSACS reliability dataset (n=23, 3 sessions)
Age, (y)	35.0±13.5 (16-61)	35.0±11.0 (27-57)
Sex, n (%)		
Men	27 (47.4)	11 (47.8)
Women	30 (52.6)	12 (52.2)
Homozygous, n (%)	52 (92.8) n=56	23 (100)
SARA (0-40)	19±14 (4-36) n=56	20.5±10.6 (7-36)
NHPT (s)	29.7±33.7 (23.9-144.9) n=56	45.3±18.4 (23.9-105.5)
SFNT (# of repetitions)	10.4±4 (5.8-21.3)	10.5±4.3 (6.0-21.3)
Grip strength (kg)	29.2±15.9 (17.2-59.1) n=55	24.7±16.6 (17.2-59.1)
Pinch strength (kg)	5.7±2.2 (3.3-10.3) n=55	5.8±1.9 (3.3-9.2) n=22
LEMOCOT (# of repetitions)	19.0±15.3 (1-48) n=49	18.5±6.0 (1-40) n=18
Barthel index (0-100)	90±20 (35-100) n=54	85.0±27.5 (45-100) n=21

Values reported as median ±interquartile range (minimum-maximum). If missing values were present, n denotes the number of participants without missing values. ARSACS: Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay. LEMOCOT: Lower Extremity Motor Coordination Test. NHPT: Nine Hole Peg Test. SFNT: Standardized Finger-Nose Test. SARA: Scale for the Assessment and Rating of Ataxia. VPIT: Virtual Peg Insertion Test.

Concurrent validity

The hypothesis related to the expected correlations with the Nine Hole Peg Test was partially fulfilled, as significant moderate correlations were found with metrics describing movement control (*SPARC return* $\rho=-0.32$, $p=0.017$ and *velocity max. return* $\rho=0.46$, $p=0.0004$), but no significant correlations were observed with metrics describing grip force control. The hypothesis related to the expected correlations with the Standardized Finger-Nose Test was fulfilled, as significant moderate correlations were observed with metrics describing movement control (*SPARC return* $\rho=-0.39$, $p=0.003$ and *velocity max. return* $\rho=-0.51$, $p<0.0001$). The hypothesis related to the expected correlations with grip strength was fulfilled, as no significant correlations were observed. The hypothesis related to the expected correlations with pinch strength was partially fulfilled, as no significant correlations with metrics of grip force control were observed, but instead a significant correlation with a metric of arm control (*velocity max. return* $\rho=-0.39$, $p=0.0039$). The hypothesis related to the expected correlations with the LEMOCOT was not fulfilled, as significant correlations were observed with metrics of arm control (*velocity max. return* $\rho=-0.32$, $p=0.021$) and grip force control (*grip force rate num. peaks transport* $\rho=-0.53$, $p<0.0001$ and *grip force rate SPARC transport* $\rho=-0.39$, $p=0.0044$). The hypothesis related to the expected correlations with the Barthel index was fulfilled, as no significant correlations were observed. Thus, overall, three hypotheses related to the concurrent validity of the VPIT metrics were fulfilled, two partially fulfilled, and one not fulfilled.

Table 2 Evaluation of reliability and learning effects of the Virtual Peg Insertion Test (VPIT) metrics considering five task repetitions and three repeated assessment sessions.

Digital health metrics	Reliability (5 VPIT repetitions)		Learning effects (5 VPIT repetitions)	
	ICC [CI]	SRD%	Norm. slope η (session 1 & 2)	Norm. slope η (session 2 & 3)
Log jerk transport	0.86 [0.81, 0.90]	32.89	1.31	-0.11
Log jerk return	0.92 [0.89, 0.94]	27.51	-2.33	2.97
SPARC return	0.93 [0.90, 0.95]	25.42	0.20	0.14
Path length ratio transport	0.80 [0.73, 0.86]	44.08	-2.36	3.48
Path length ratio return	0.62 [0.48, 0.73]	45.23	-2.95	-2.68
Velocity max. return	0.90 [0.86, 0.93]	23.84	3.25	-5.07*
Jerk peg approach	0.33 [0.09, 0.52]	55.48	-1.84	-0.09
Grip force rate num. peaks transport	0.82 [0.76, 0.87]	28.92	0.00	0.00
Grip force rate SPARC transport	0.91 [0.88, 0.94]	19.14	-1.42	-0.14
Grip force rate hole approach	0.88 [0.83, 0.91]	34.55	-1.25	-4.29

ICC: intra-class correlation. CI: confidence interval. SRD%: smallest real difference. * $p < 0.05$, ** $p < 0.001$ for paired t-test between sessions. For all three statistics, accepted cut-offs (ICC > 0.7 , SRD% < 30.3 , $\eta > -6.35$ or non-significant) were used to determine if a metric fulfils each of the evaluation criteria (values in bold font)

Table 3 Concurrent validity (Spearman correlations) between VPIT digital health metrics and clinical assessments.

Digital health metrics	Clinical assessments					
	Nine Hole Peg Test	Standardized Finger to Nose Test	Grip strength	Pinch strength	Lower Extremity Motor Coordination Test	Barthel index
Log jerk transport	0.15	-0.18	-0.23	-0.15	-0.01	-0.08
Log jerk return	0.20	-0.11	-0.12	-0.01	0.16	0.11
SPARC return	-0.32*	-0.39*	-0.24	-0.1	0.01	-0.1
Path length ratio transport	0.25	-0.16	-0.04	0.00	0.05	-0.12
Path length ratio return	0.17	-0.13	-0.27	-0.01	0.16	0.00
Velocity max. return	0.46**	-0.51**	-0.21	-0.39*	-0.32*	-0.24
Jerk peg approach	0.10	0.04	-0.15	-0.1	0.09	0.09
Grip force rate num. peaks transport	0.21	-0.18	-0.13	-0.21	-0.53**	0.00
Grip force rate SPARC transport	0.26	-0.24	0.04	-0.16	-0.39*	-0.15
Grip force rate hole approach	0.21	-0.06	-0.12	-0.10	-0.14	-0.09
	<i>Hypothesis partially fulfilled</i>	<i>Hypothesis fulfilled</i>	<i>Hypothesis fulfilled</i>	<i>Hypothesis partially fulfilled</i>	<i>Hypothesis not fulfilled</i>	<i>Hypothesis fulfilled</i>

* $p < 0.05$, ** $p < 0.001$. SPARC: spectral arc length.

Discussion

The aim of this work was to document metrological properties of a previously established core set of 10 digital health metrics extracted from the VPIT, a technology-aided assessment of upper limb movement patterns and grip force control, and ensure that those can be used as novel, insightful clinical endpoints for studies in persons with ARSACS.

The need for novel, sensitive, and fine-grained assessments of upper limb coordination in ARSACS is exemplified by a longitudinal study that relied on clinical scales and observed that, over a 2-year period, lower limb coordination, balance, walking abilities, and overall disease severity, but not upper limb coordination, deteriorated significantly [33]. This is surprising, given that it is expected that the significant deterioration in these body functions reflect pathological changes in the pyramidal and cerebellar systems that should also impact upper limb coordination. Hence, it was speculated that the absence of significant deterioration in upper limb coordination was mainly an artifact of the available outcome measures [33]. These included the Nine Hole Peg Test, which seems to not be sensitive enough to detect fine alterations in motor control, especially in persons that show considerable impairments in upper limb distal strength [33].

Eight VPIT metrics are well-suited for cross-sectional studies in persons with ARSACS

We found that eight of the VPIT core metrics have excellent test-retest reliability and five have relatively low measurement error across three assessment sessions. In addition, none of the metrics has strong learning effects across sessions, with only a slight improvement in speed visible between sessions two and three that was below the established cut-off. This provides evidence that eight VPIT metrics have robust statistical properties to accurately and objectively characterize sensorimotor impairments in cross-sectional studies in persons with ARSACS. Further, this establishes the foundation for the integration of five VPIT metrics as potentially sensitive endpoints in longitudinal studies. In the future, the responsiveness of the VPIT metrics should be fully evaluated, for example by capturing longitudinal changes in sensorimotor impairments and comparing them to the herein established smallest real difference values [34]. The relatively high measurement error in certain metrics likely results from the ability of technology-aided to capture behavioral variability in task execution, which would have not been covered by clinical scales [17].

Further, we observed that a reduction of the number of repetitions in the assessment protocol can be achieved without large changes in the metrological properties of the metrics, except for the *jerk approach peg* metric, which was anyways deemed as not reliable in the first place. However, slight changes in the measurement error of two metrics led them to be slightly above the defined cut-off. Given that the measurement error is mainly relevant when longitudinally assessing sensorimotor impairments, this does not affect the applicability of the metrics for cross-sectional studies. Thus, these results further increase the clinical feasibility of the VPIT, making it applicable in approximately 10 minutes per body side, which comes at an acceptable reduction in the robustness of the VPIT metrics that are relevant in ARSACS. This

is an important result, as time constraints have been identified as one of the key factors hindering the clinical integration of technology-aided assessments [14].

For the test-retest reliability analysis, the obtained metrological properties are in general in line with the values reported in literature [5, 30]. Interestingly, in the previous evaluation of the VPIT metrics in post-stroke population, four out of the 10 core metrics showed considerable learning effects across sessions [17]. On the contrary, no strong learning effects were observed in persons with ARSACS, suggesting that they could successfully learn the task already within the first training and repetitions of the task. Reasons for this might be that post-stroke population are typically of older age and have stronger cognitive impairment than ARSACS population [35]. This highlights the importance of evaluating the sensor-based metric separately for each envisioned target population, which is rarely implemented for infrequent diseases such as ARSACS.

Interestingly, the metrics *jerk peg approach* and *path length ratio return* had suboptimal reliability and measurement error values, which has also been observed in chronic post-stroke performing the VPIT (Kanzler et al 2020). Given that similar metrics reported during other phases of the task had excellent statistical properties (e.g., *path length ratio transport* or *log jerk transport*), it is likely that task-related variability leads to these results and not the mathematical definition of the metrics per se. This emphasizes that it is challenging to recommend specific metrics that are statistically valid for all technology-aided assessments and that instead data-driven selection approaches should be leveraged to define to a core set of robust metrics for each task [11]

The VPIT metrics are valid descriptors of upper limb coordination in ARSACS

The analysis of concurrent validity suggests that three of the initially formed hypotheses were fulfilled (SFNT, grip strength, Barthel), two partially fulfilled (NHPT, pinch strength), and one not fulfilled (LEMOCOT). Overall, the correlations between the VPIT metrics and the clinical scales were low to moderate, which is line with similar analysis performed in literature evaluating sensor-based metrics in neurological disorders [5, 17, 30]. This highlights that sensor-based metrics and clinical scores are related, but not redundant, thereby emphasizing their value as complementary endpoints that can help to provide novel insights into sensorimotor impairments in ARSACS.

As expected, two kinematic VPIT metrics describing gross movements (SPARC return, velocity max return) correlated moderately with the NHPT and the SFNT, thereby confirming that these metrics capture aspects of fine and gross upper limb coordination. However, we would also have expected a correlation between the kinetic VPIT metrics and the NHPT, given that both assess components of grip force control. The low correlation therein might be because the VPIT requires a power grip and the NHPT a precision grip. Also, the absence of a correlation between the kinetic VPIT metrics and the NHPT might be because the NHPT only provides one compound outcome measure describing both movement and grip force control.

We expected low correlations between the digital health metrics and indicators of grip/pinch strength, given that different body systems are involved in precise grip force control (VPIT metrics) and grip strength (clinical scores) [31, 36]. However, a modest correlation between VPIT digital health metrics describing speed during goal-directed movements with pinch strength was observed. This might indicate that impairments in arm movements and grip strength are similarly affected by disease severity in ARSACS.

Further, we observed moderate significant correlations between three digital health metrics (movement speed during return and grip force control during transport) and the LEMOCOT, an assessment of lower limb coordination. These correlations were more consistent and pronounced than the ones observed with the clinical upper limb functional tasks, such as the NHPT and the SFNT. This could be explained by a shared physiological mechanism of disrupted lower and upper limb coordination in ARSACS, which is of cerebellar origin [21, 22]. This suggests that the impairment-based metrics of the VPIT are indeed able to inform on suboptimal motor control, whereas the activity-based assessment of the NHPT and SFNT capture the effect of these impairments on a functional level.

As expected, no considerable correlations between the VPIT digital health metrics and independence in daily life, as measured by the Barthel index, were found. This is likely because the included persons with ARSACS still had overall high levels of independence (Barthel index values 90 ± 20 , scale maximum at 100).

Conclusions

This work provides evidence for the robustness and validity of eight sensor-based digital health metrics of the VPIT as insightful endpoints that objectively characterize upper limb movement patterns and grip forces in persons with ARSACS. In addition, five of the metrics have well-suited statistical properties to serve as potentially sensitive endpoints in longitudinal studies. Further, an adapted protocol of the VPIT with three instead of five task repetitions was successfully established, thereby further enhancing the clinical feasibility of the VPIT. This opens up novel avenues for thoroughly studying impaired upper limb coordination in ARSACS and to reconsider the temporal evolution of upper limb sensorimotor impairments in persons with ARSACS in the future.

Declarations

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

The authors would like to thank all study participants. The study was funded by the Canadian Institutes of Health Research (Emerging Team Grant no TR2-119189), Fondation de l'Ataxie Charlevoix-Saguenay,

and Muscular Dystrophy Canada. Additionally, the research was conducted as part of the Future Health Technologies programme which was established collaboratively between ETH Zurich and the National Research Foundation Singapore. This research is supported by the National Research Foundation, Prime Minister's Office, Singapore under its Campus for Research Excellence and Technological Enterprise (CREATE) programme. CG holds a career-grant funding from Fonds de recherche du Québec- santé (no 31011).

The authors declare that the funding bodies did not influence the design of the study, the collection, analysis, and interpretation of data, and the writing of the manuscript.

References

1. Synofzik M, Soehn AS, Gburek-Augustat J, et al (2013) Autosomal recessive spastic ataxia of Charlevoix Saguenay (ARSACS): Expanding the genetic, clinical and imaging spectrum. *Orphanet J Rare Dis* 8:. <https://doi.org/10.1186/1750-1172-8-41>
2. Engert JC, Bérubé P, Mercier J, et al (2000) ARSACS, a spastic ataxia common in northeastern Quebec, is caused by mutations in a new gene encoding an 11.5-kb ORF. *Nat Genet* 24:120–125. <https://doi.org/10.1038/72769>
3. Schmitz-Hübsch T, du Montcel ST, Baliko L, et al (2006) Scale for the assessment and rating of ataxia. *Neurology* 66:1717 LP – 1720. <https://doi.org/10.1212/01.wnl.0000219042.60538.92>
4. Mathiowetz V, Weber K, Kashman N, Volland G (1985) Adult Norms for the Nine Hole Peg Test of Finger Dexterity. *Occup Ther J Res* 5:24–38. <https://doi.org/10.1177/153944928500500102>
5. Schwarz A, Kanzler CM, Lambercy O, et al (2019) Systematic Review on Kinematic Assessments of Upper Limb Movements After Stroke. *Stroke* 50:718–727. <https://doi.org/10.1161/STROKEAHA.118.023531>
6. Scott SH, Dukelow SP (2011) Potential of robots as next-generation technology for clinical assessment of neurological disorders and upper-limb therapy. *J Rehabil Res Dev* 48:335. <https://doi.org/10.1682/jrrd.2010.04.0057>
7. Krebs HI, Krams M, Agrafiotis DK, et al (2014) Robotic measurement of arm movements after stroke establishes biomarkers of motor recovery. *Stroke* 45:200–204. <https://doi.org/10.1161/Strokeaha.113.002296/-/DC1>
8. Coderre AM, Amr Abou Zeid, Dukelow SP, et al (2010) Assessment of Upper-Limb Sensorimotor Function of Subacute Stroke Patients Using Visually Guided Reaching. *Neurorehabil Neural Repair* 24:528–541. <https://doi.org/10.1177/1545968309356091>
9. Colombo R, Member S, Sterpi I, et al (2010) Measuring changes of movement dynamics during robot-aided neurorehabilitation of stroke patients. *IEEE Trans Neural Syst Rehabil Eng* 18:75–85. <https://doi.org/10.1109/TNSRE.2009.2028831>
10. Gagnon C, Lavoie C, Lessard I, et al (2014) The Virtual Peg Insertion Test as an assessment of upper limb coordination in ARSACS patients: A pilot study. *J Neurol Sci* 347:341–344.

<https://doi.org/10.1016/j.jns.2014.09.032>

11. Kanzler CM, Rinderknecht MD, Schwarz A, et al (2020) A data-driven framework for selecting and validating digital health metrics: use-case in neurological sensorimotor impairments. *npj Digit Med* 3:80. <https://doi.org/10.1038/s41746-020-0286-7>
12. Prinsen CAC, Mokkink LB, Bouter LM, et al (2018) COSMIN guideline for systematic reviews of patient-reported outcome measures. *Qual Life Res* 27:1147–1157. <https://doi.org/10.1007/s11136-018-1798-3>
13. Frykberg GE, Grip H, Murphy MA (2021) How many trials are needed in kinematic analysis of reach-to-grasp?—A study of the drinking task in persons with stroke and non-disabled controls. *J Neuroeng Rehabil* 18:1–13. <https://doi.org/10.1186/s12984-021-00895-3>
14. Shirota C, Balasubramanian S, Melendez-Calderon A (2019) Technology-aided assessments of sensorimotor function: current use, barriers and future directions in the view of different stakeholders. *J Neuroeng Rehabil* 16:53. <https://doi.org/10.1186/s12984-019-0519-7>
15. Fluet MC, Lamercy O, Gassert R (2011) Upper limb assessment using a Virtual Peg Insertion Test. *IEEE Int Conf Rehabil Robot*. <https://doi.org/10.1109/ICORR.2011.5975348>
16. Kanzler CM, Schwarz A, Held J, et al (2020) Technology-aided assessment of functionally relevant sensorimotor impairments in arm and hand of post-stroke individuals. *J Neuroeng Rehabil* 5:1–15. <https://doi.org/10.1101/2020.04.16.044719>
17. Kanzler CM, Schwarz A, Held J, et al (2020) Technology-aided assessment of functionally relevant sensorimotor impairments in arm and hand of post-stroke individuals. *J Neuroeng Rehabil* 17:128. <https://doi.org/https://doi.org/10.1101/544601>
18. Balasubramanian S, Melendez-Calderon A, Burdet E (2012) A robust and sensitive metric for quantifying movement smoothness. *IEEE Trans Biomed Eng* 59:2126–2136. <https://doi.org/10.1109/TBME.2011.2179545>
19. Rohrer B, Fasoli S, Krebs HI, et al (2002) Movement smoothness changes during stroke recovery. *J Neurosci Off J Soc Neurosci* 22:8297–8304. <https://doi.org/22/18/8297> [pii]
20. Cirstea MC, Levin MF (2000) Compensatory strategies for reaching in stroke. *Brain* 123:940–53. <https://doi.org/10.1093/brain/123.5.940>
21. Manto M (2009) Mechanisms of human cerebellar dysmetria: Experimental evidence and current conceptual bases. *J Neuroeng Rehabil* 6:1–18. <https://doi.org/10.1186/1743-0003-6-10>
22. Manto M, Bower JM, Conforto AB, et al (2012) Consensus paper: Roles of the cerebellum in motor control—the diversity of ideas on cerebellar involvement in movement. *Cerebellum* 11:457–487. <https://doi.org/10.1007/s12311-011-0331-9>
23. Mathiowetz V, Weber K, Volland G, Kashman N (1984) Reliability and validity of grip and pinch strength evaluations. *J Hand Surg Am* 9:222–226. [https://doi.org/10.1016/S0363-5023\(84\)80146-X](https://doi.org/10.1016/S0363-5023(84)80146-X)
24. Gagnon C, Mathieu J, Desrosiers J (2004) Standardized finger-nose test validity for coordination assessment in an ataxic disorder. *Can J Neurol Sci* 31:484–489. <https://doi.org/10.1017/S031716710000367X>

25. Lessard I, Lavoie C, Côté I, et al (2017) Validity and reliability of the LEMOCOT in the adult ARSACS population: A measure of lower limb coordination. *J Neurol Sci* 377:193–196.
<https://doi.org/10.1016/j.jns.2017.03.046>
26. Mahoney FI (1965) Functional evaluation: the Barthel index. *Md State Med J* 14:61–65
27. de Vet HCW, Terwee CB, Knol DL, Bouter LM (2006) When to use agreement versus reliability measures. *J Clin Epidemiol* 59:1033–1039. <https://doi.org/10.1016/j.jclinepi.2005.10.015>
28. Beckerman H, Roebroeck ME, Lankhorst GJ, et al (2001) Smallest real difference, a link between reproducibility and responsiveness. *Qual Life Res* 10:571–578.
<https://doi.org/10.1023/A:1013138911638>
29. Martin Bland J, Altman D (1986) Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 327:307–310. [https://doi.org/10.1016/S0140-6736\(86\)90837-8](https://doi.org/10.1016/S0140-6736(86)90837-8)
30. Tran V Do, Dario P, Mazzoleni S (2018) Kinematic measures for upper limb robot-assisted therapy following stroke and correlations with clinical outcome measures: A review. *Med Eng Phys* 53:13–31.
<https://doi.org/10.1016/j.medengphy.2017.12.005>
31. Allgöwer K, Hermsdörfer J (2017) Fine motor skills predict performance in the Jebsen Taylor Hand Function Test after stroke. *Clin Neurophysiol* 128:1858–1871.
<https://doi.org/10.1016/j.clinph.2017.07.408>
32. Xu J, Ejaz N, Hertler B, et al (2017) Separable systems for recovery of finger strength and control after stroke. *J Neurophysiol* 118:1151–1163. <https://doi.org/10.1152/jn.00123.2017>
33. Gagnon C, Lessard I, Lavoie C, et al (2018) An exploratory natural history of ataxia of charlevoix-saguenay a 2-year follow-up. *Neurology* 91:E1307–E1311.
<https://doi.org/10.1212/WNL.0000000000006290>
34. Schuck P, Zwingmann C (2003) The “smallest real difference” as a measure of sensitivity to change: A critical analysis. *Int J Rehabil Res* 26:85–91. <https://doi.org/10.1097/00004356-200306000-00002>
35. Tham W, Auchus AP, Thong M, et al (2002) Progression of cognitive impairment after stroke. *J Neurol Sci* 203–204:49–52. [https://doi.org/10.1016/S0022-510X\(02\)00260-5](https://doi.org/10.1016/S0022-510X(02)00260-5)
36. Lindberg PG, Roche N, Robertson J, et al (2012) Affected and unaffected quantitative aspects of grip force control in hemiparetic patients after stroke. *Brain Res* 1452:96–107.
<https://doi.org/10.1016/j.brainres.2012.03.007>

Supplementary Materials

Table SM1 Reliability and learning effects of the VPIT metrics considering 3 task repetitions.

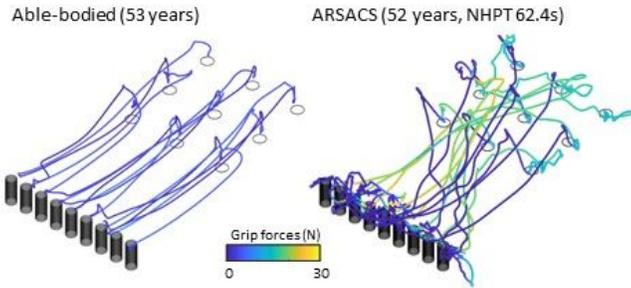
Digital health metrics	Reliability (3 VPIT repetitions)		Learning effects (3 VPIT repetitions)	
	ICC [CI]	SRD%	Norm. slope η (session 1 & 2)	Norm. slope η (session 2 & 3)
Log jerk transport	0.82 [0.74, 0.89]	33.64	2.76	4.28
Log jerk return	0.88 [0.81, 0.92]	31.26	3.95	-4.07
SPARC return	0.92 [0.88, 0.95]	26.75	0.17	-4.05
Path length ratio transport	0.74 [0.61, 0.83]	43.58	-2.68	1.31
Path length ratio return	0.35 [0.03, 0.57]	44.91	-4.57	-0.23
Velocity max. return	0.88 [0.82, 0.92]	25.94	2.80	-8.46
Jerk peg approach	0.03 [-0.45, 0.37]	87.75	-1.33	-0.04
Grip force rate num. peaks transport	0.74 [0.61, 0.83]	31.72	0.00	0.00
Grip force rate SPARC transport	0.89 [0.84, 0.93]	22.97	2.50	-2.70
Grip force rate hole approach	0.85 [0.78, 0.90]	34.55	-3.77	-0.42

Figures

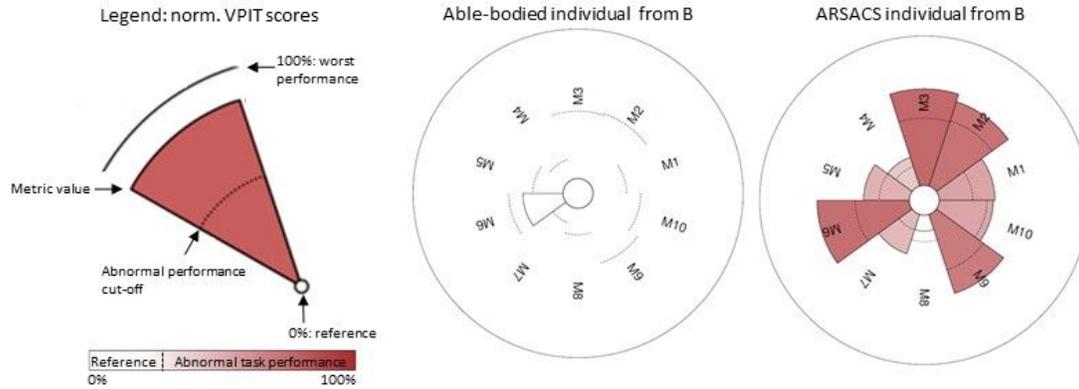
A: Virtual Peg Insertion Test (VPIT)



B: Representative movement & grip force patterns



C: Objective multi-dimensional profiles of arm and hand impairments



D: Study protocol

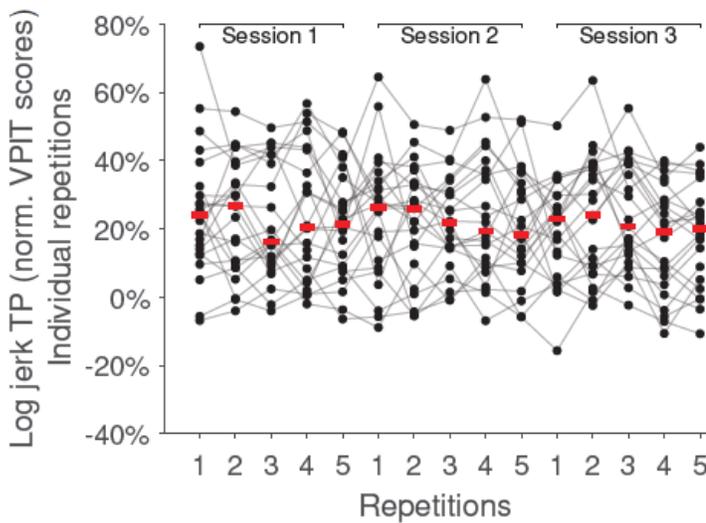


Figure 1

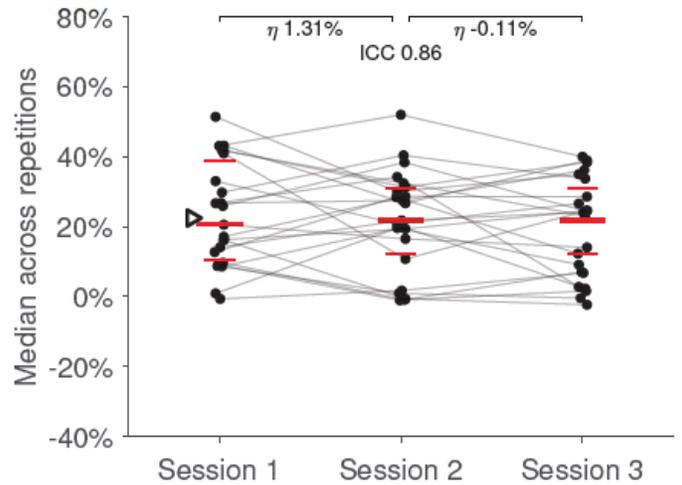
Overview of the Virtual Peg Insertion Test (A), the collected kinematic and kinetic data (B), the processed impairment profiles relying on 10 sensor-based digital health metrics (C, M1-10) data, as well as the study protocol (D). In panel B, the able-bodied participant is a 53 years old female, whereas the ARSACS participant is a 52 years old male with a NHPT score of 62.4s. In the middle and right part of panel C, each pie segment represents the value of one sensor-based digital health metric extracted from the VPIT

data of the participants in panel B. The left part of panel C provides the legend for the visualization. In more details, the metrics are normalized on the range $]-\infty, +\infty[$, with 0% (inner radius of the circle) indicating the median of an able-bodied reference population and 100% (outer radius of the circle) the worst neurological subject in the VPIT database. For visualization, values below 0% (i.e., better than the reference population) are not displayed. The dashed circular line indicates the 95th-percentile of the reference population, which is used to define abnormal task performance. Abbreviations: ARSACS: Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay. NHPT: Nine Hole Peg Test. M1-M10: M1: log jerk transport. M2: log jerk return. M3: SAL return. M4: path length ratio transport. M5: path length ratio return. M6: velocity max return. M7: jerk peg approach. M8: force peaks transport. M9: force rate SAL transport. M10: force rate SAL hole approach. SAL: spectral arc length.

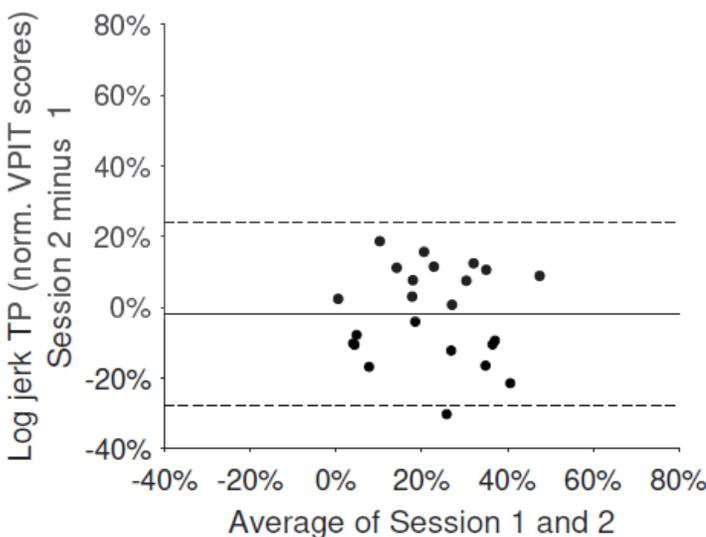
A: Variability across repetitions



B: Variability across sessions



C: Bland-Altman analysis



D: Intra-subject variability

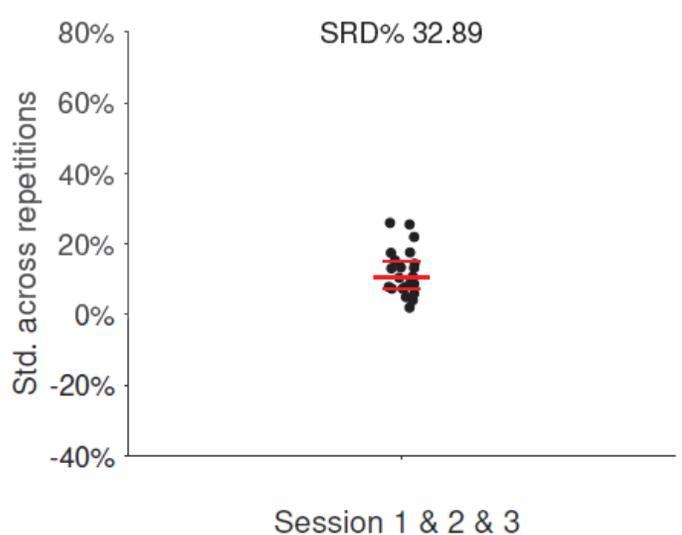


Figure 2

Evaluation of the VPIT metrics in ARSACS: example of the log jerk transport as an indicator of movement smoothness. The variability of the metrics across repetitions (A) and sessions (B) to investigate the presence of learning effects (slope η between sessions, normalized relative to range of values) and the ability of a metric to discriminate across participants (intra-class correlation coefficient, ICC). In addition, a Bland-Altman analysis (C, solid and dashed horizontal lines represent the median and 5th- & 95th-percentile of differences, respectively) was performed to check for systematic bias. Lastly, the intra-participant variability and the closely related measurement error (D, smallest real difference, SRD%) of a metric were characterized. Horizontal red bars indicate 25th-, 50th-, and 75th- percentile of the characterized distribution. The triangle in panel B defines the 95th-percentile of control participants, which is commonly used as a cut-off to identify individuals with abnormal task performance. ARSACS: Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay. Log: logarithm. TP: Transport.