Movement Disorders
CLINICAL PRACTICE

BRIEF REPORT

Pediatric Huntington Disease Brains Have Distinct Morphologic and Metabolic Traits: the RAREST-JHD Study

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ABSTRACT: Background: Pediatric-onset Huntington's disease (POHD) exhibits a phenotype different from adult-onset HD (AOHD), with hypokinetic movement disorders (eg, rigidity, bradykinesia, and dystonia) rather than chorea typical of AOHD.
Objectives: The aim was to identify pathophysiology-based biomarkers specific to POHD (≥60 CAG repeats).
Methods: Simultaneous hybrid imaging using [^{18}F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography plus magnetic resonance imaging (FDG-PET/MRI) and clinical assessment using standardized Huntington's disease (HD) scales were employed. Exploratory longitudinal analyses were also performed.
Results: Striatal volume loss was remarkable and more severe in POHD (n = 5) than in AOHD (n = 14). Widespread, significantly altered glucose metabolism occurred in several different POHD cortical areas and thalamus, but not AOHD cortex, consistent with differences in clinical progression.
Conclusions: POHD patients' brains exhibited distinct morphologic and metabolic traits compared to AOHD patients' brains, with longitudinal changes mirroring clinical progression. Hybrid FDG-PET/MRI highlighted a variable regional brain dysfunction in vivo, as a biological consequence of highly expanded CAG repeats. Findings provide further evidence that POHD is a distinct disease from AOHD.

Huntington's disease (HD) is caused by expanded CAG repeat mutations (>35 CAGs) in the *huntingtin* gene (*HTT*).[1,2] Patients usually present in adulthood, but symptoms manifest before 21 years in 4% to 10% of cases (juvenile-onset HD [JOHD]).[3,4] Expanded CAG repeat numbers overlap between adult-onset HD (AOHD) and JOHD,[5] but rare occurrences of highly expanded repeats (>55–60 CAG) are clearly associated with the rarest pediatric-onset HD (POHD; age of onset <18 years) form.[4,6] Motor manifestations of POHD, namely hypokinetic movement disorders with variable rigidity, bradykinesia, and dystonia, are different from typical AOHD symptoms (ie, chorea).[3–6] POHD also differs from JOHD and AOHD in terms of lower levels of glucose transporters, abnormal expression of markers of energy metabolism, altered cortical mitochondrial machinery, and abnormal patterns of brain dysfunction and degeneration, highlighting biological mechanisms specific to this form of the disease.[6,7] POHD may therefore require a different treatment approach and the identification of distinct biomarkers for monitoring disease progression. Imaging studies integrating glucose metabolism and regional brain volumes could identify such POHD-specific biomarkers for use in HD trials. We therefore compared clinical characteristics of POHD and AOHD patients alongside regional brain volumes and glucose metabolism, using simultaneous

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Keywords: glucose metabolism, magnetic resonance imaging (MRI), pediatric-onset Huntington's disease, positron emission tomography (PET), striatal volume, simultaneous imaging.

Received 21 April 2024; revised 17 August 2024; accepted 20 September 2024.
Published online 00 Month 2024 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.14223

hybrid [^{18}F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography and magnetic resonance imaging (PET/MRI).

Patients and Methods

Study Design

RAREST-JHD was a 3-year prospective study (June 19, 2019, to October 1, 2022)[8] assessing clinical, genetic, and imaging characteristics of young HD patients to identify potential biomarkers of diseases.[6,7]

Patients

We included adult patients (aged >18 years) previously diagnosed with POHD (adolescent onset) with a *HTT* mutation >60 CAG repeats and adult patients previously diagnosed with AOHD (adult onset) with a *HTT* mutation <60 CAG repeats. All patients were included in the ENROLL-HD platform, a worldwide HD observational initiative.[9] RAREST-JHD excluded patients with severe psychiatric manifestations and included AOHD patients matched for disease duration.

Baseline Clinical Assessment

All patients underwent neurological and neuropsychological evaluation using the Unified Huntington's Disease Rating Scale,[10] according to the ENROLL-HD protocol[9] (Supplementary Material in Data S1).

Baseline Image Acquisition

All patients underwent hybrid [^{18}F]FDG-PET/MRI on a 3T scanner (Siemens Biograph mMR, Siemens Healthcare, Erlangen, Germany) at the University of Catanzaro, Italy (Supplementary Material in Data S1).

Longitudinal Follow-Up

Patients were followed up annually for 2 years. All baseline clinical and imaging assessments were repeated at follow-up visits and performed as closely together as possible. Longitudinal changes in clinical and imaging variables (cortical thickness, subcortical volumes, PVC (Partial Volume Correction) -uptake values) were calculated as a percentage of baseline value according to the following formula:

$$\text{Yearly\%change} = 100 \times \left(\frac{\text{value}_{tp1} - \text{value}_{tp2}}{\text{value}_{tp1}}\right) \times \frac{12}{\text{follow} - \text{up duration in months}}$$

Due to the small sample size, longitudinal analyses should be considered exploratory only.

Statistical Analysis

Statistics was performed using *R* (version 4.0.2). Sex distributions were compared using χ^2, and continuous measures were compared using *t*-test or Mann–Whitney *U*-test, according to Shapiro's normality test. Structural and metabolic measures were compared using analysis of covariance, with age, sex, and intracranial volume as covariates. Multiple comparisons were accounted for using false discovery rate (FDR, adjusted P_{FDR} <0.05). Post hoc Spearman's correlations investigated associations between clinical scores and PET/MRI measures (adjusted P_{FDR} <0.05).

Results

Patients

We screened 21 patients for eligibility, and 2 were excluded due to *HTT* mutation homozygosity. Five patients met the inclusion criteria for POHD, and 14 met the inclusion criteria for AOHD (cross-sectional cohort, N = 19). Of these, 3 POHD and 6 AOHD patients completed follow-up (longitudinal cohort, n = 9). Mean follow-up duration was 17 months.

Baseline demographics and clinical characteristics showed significant difference in age, age of onset, CAG repeats, and CAG-age-product (CAP) score between POHD and AOHD cross-sectional cohorts (Table 1). Total Motor Scores (TMS) and cognitive scores were not statistically different between the 2 cohorts, indicating similar clinical severity. However, baseline parkinsonism subitem scores were higher in JOHD than AOHD (median [range]: 4.0 [2–4] and 2.0 [0–3], respectively, $P = 0.003$).

Demographic and clinical characteristics for the longitudinal cohort are presented in Table S1. The JOHD and AOHD groups exhibited similar rates of disease progression, as measured by changes in TMS, and Total Functional Capacity (TFC), Independence Scale, and Mini-Mental State Examination scores at follow-up (Table S1).

Brain Volume and Glucose Uptake at Baseline

Total intracranial volume (1.42 ± 0.16 vs. $1.35 \pm 0.10 \times 10^6$ mm^3) and whole-brain FDG uptake (0.61 ± 0.04 vs. $0.59 \pm 0.03 \times 10^6$ mm^3) did not differ between POHD and AOHD, respectively. When all patients were considered, age correlated positively with increasing striatal volume (left $\rho = 0.68$, right $\rho = 0.64$), reflecting early striatal volume loss in POHD. Conversely, age correlated negatively with cortical thickness in frontoparietal regions, namely the right frontal pole ($\rho = -0.69$), rostral middle frontal gyrus ($\rho = -0.75$), left pars orbitalis ($\rho = -0.69$), and bilateral postcentral gyri (left $\rho = -0.74$, right $\rho = -0.72$).

Volumes of striatal structures (putamen, caudate, nucleus accumbens, and globus pallidus) were significantly lower in POHD versus AOHD patients (Fig. 1A), paralleled by significantly

TABLE 1 *Baseline demographic and clinical characteristics of the cross-sectional cohort (N = 19)*

Items	POHD (n = 5)	AOHD (n = 14)	*P*-value
Baseline			
Age (years), mean ± SD [range]	24.2 ± 5.7 [20–34]	45.1 ± 10.7 [28–62]	**<0.001**[a]
Sex (n females)	4	8	**0.02**[b]
Age at onset (years), median [range]	16.0 [15–18]	42.5 [21–54]	**<0.001**[c]
Disease duration (years), median [range]	5 [4–18]	5 [1–13]	0.57[c]
HD stage, median [range]	3 [2–4]	2 [1–3]	0.07[b]
CAG repeats (n), median [range]	60 [59–67]	43 [40–56]	**0.001**[c]
CAP score, median [range]	633.6 [558.8–897.6]	465.3 [362.6–739.2]	**0.004**[c]
TMS, median [range]	42.0 [32–93]	29.5 [11–73]	0.23[c]
TFC Scale score, mean ± SD [range]	5.5 ± 3.1 [1–8]	9.9 ± 2.5 [4–13]	0.06[a]
IS score, median [range]	70.0 [40–75]	80.0 [45–100]	0.67[c]
MMSE score, median [range]	25.0 [24–26]	26.5 [18–29]	0.34[c]
SDMT score, mean ± SD [range]	21.3 ± 4.2 [18–26]	27.6 ± 13.4 [9–51]	0.19[a]
SVF score, mean ± SD [range]	12.0 ± 3.6 [9–16]	12.6 ± 5.1 [7–21]	0.81[a]
SCN score, mean ± SD [range]	52.0 ± 2.6 [50–55]	49.2 ± 20.0 [22–78]	0.62[a]
SWR score, mean ± SD [range]	75.7 ± 1.5 [74–77]	65.0 ± 25.2 [27–103]	0.13[a]

Note: *p*-values are in bold.
Higher scores on the TMS indicate more severe motor impairment, whereas higher sores for TFC, IS, MMSE, SDMT, SVF, SCN, and SWR indicate better functional capacity, independence, or cognitive performance.
[a]Normally distributed variables are reported as mean ± SD and range, along with *P*-values relative to *t*-tests.
[b]*P*-values from χ^2 test.
[c]Nonnormally distributed variables are reported as median and range, along with *P*-values from Mann–Whitney *U*-test.
Abbreviations: POHD, pediatric-onset Huntington's disease; AOHD, adult-onset Huntington's disease; SD, standard deviation; HD, Huntington's disease; CAP, CAG-age-product; TMS, Total Motor Scale; TFC, Total Functional Capacity Scale; IS, Independence Scale; MMSE, Mini-Mental State Examination; SDMT, Symbol Digit Modality Test; SVF, Semantic Verbal Fluency; SCN, Stroop Color Naming; SWR, Stroop Word Reading; TMS, Total Motor Score.

lower glucose metabolism, as measured by FDG uptake (Fig. 1B). In contrast, FDG uptake was higher in the bilateral thalamus of POHD versus AOHD patients (Fig. 1B).

The POHD cohort had a relatively preserved brain cortex, compared with AOHD. Cortical thickness was significantly lower in AOHD versus POHD patients in bilateral insula and frontal lobe regions, namely the right rostral-anterior cingulate, frontal pole, and lateral orbitofrontal cortex (Fig. 1C).

A comparison of regional glucose metabolism showed significantly lower FDG uptake in bilateral entorhinal cortices in POHD versus AOHD patients (Fig. 1D). In contrast, AOHD patients had a significantly lower FDG uptake than POHD patients only in specific cortical regions (left inferior parietal gyrus and left cingulate gyrus).

Brain Volume and Glucose Uptake at Follow-Up

Annualized rates of volume loss were greater in all 3 POHD patients compared to the AOHD cohort in several regions (Figure S1), particularly the parietal and occipital lobes (up to 15% reduction in cortical thickness) and the caudate (up to 30% volume reduction). Both groups demonstrated ventricular enlargement, albeit more prominently in POHD (+30%) than AOHD (+10%).

Patients with AOHD exhibited widespread reduction in FDG uptake in cortical regions (annualized percentage change, −5%), whereas subcortical regions varied little. Exceptions were the right pallidum and bilateral hippocampi, with annualized increases in FDG uptake of ∼3% to 4%. In marked contrast, patients with POHD had highly variable annualized changes in FDG uptake, with striking decreases and increases across widespread cortical (−40% to +40%) and subcortical (−20% to +20%) structures (Figure S2).

Glucose Uptake in POHD and Relationship with Clinical Scores

Although brain volume changes were relatively similar among the 3 POHD patients, alterations in glucose metabolism were highly individualized, with greater annual changes in metabolism linked to more severe worsening in annualized dystonia, parkinsonism, and independence scores.

POHD patient 1 exhibited a bilateral mild decrease in FDG uptake in the fronto-occipital cortex and caudate nuclei but an

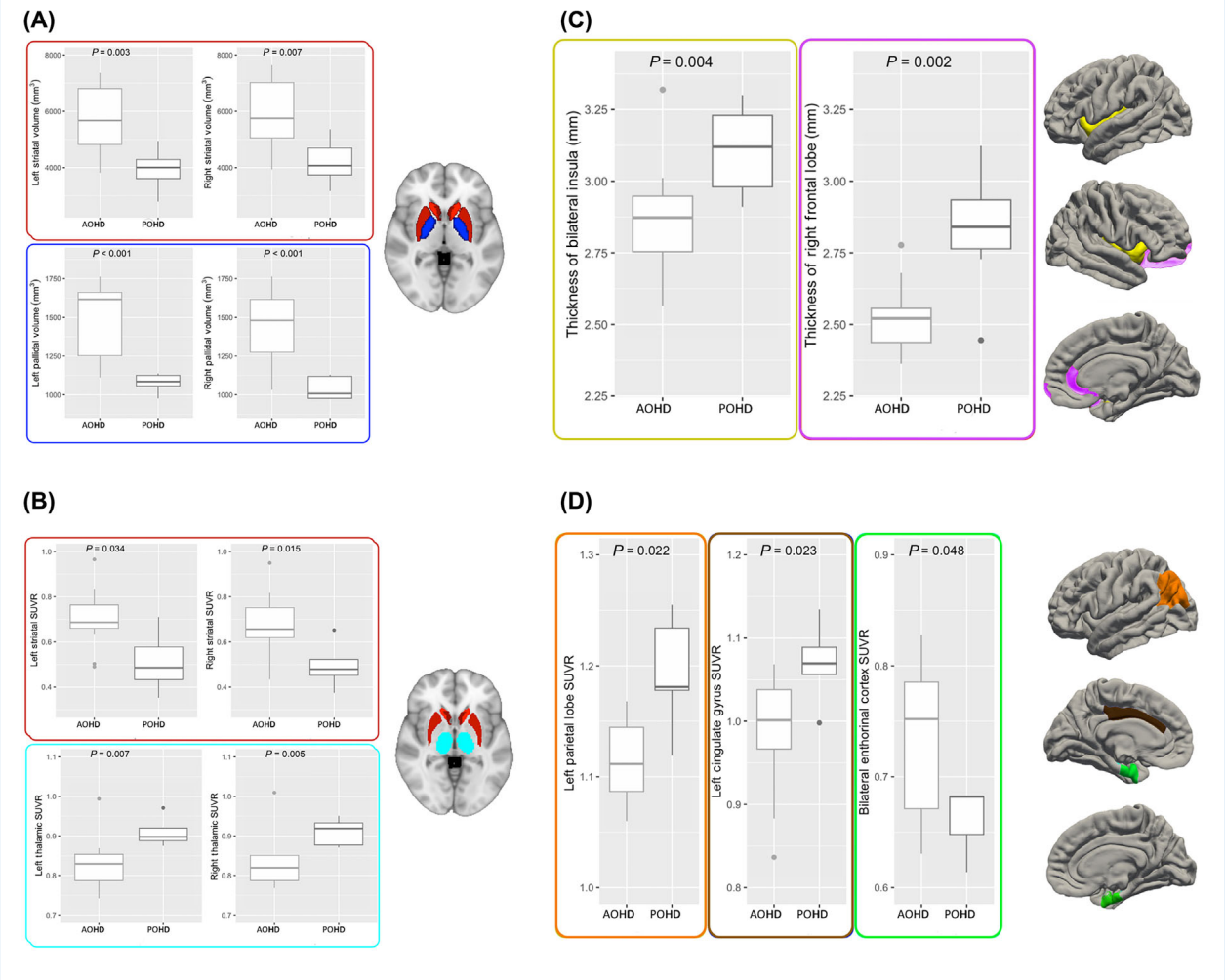

FIG. 1. FDG-PET/MRI findings in POHD (n = 5) and AOHD (n = 14) patients. Color coding: red = striatum, blue = pallidus, light blue = thalamus, yellow = insula, pink = right frontal, green = entorhinal, orange = inferior parietal, brown = cingulate. Boxes, upper and lower quartiles; lines, medians; whiskers, upper and lower extremes; dots, outliers. *t*-Test and false discovery rate correction for multiple comparisons. AOHD, adult-onset Huntington's disease; FDG-PET/MRI, [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography magnetic resonance imaging; POHD, pediatric-onset Huntington's disease. (**A**) Subcortical volume. (**B**) Subcortical FDG-PET. (**C**) Cortical thickness. (**D**) Cortical FDG-PET.

increase in temporoparietal lobes and the left thalamus (Figure S2); TMS and TFC scores were stable over 15 months.

POHD patient 2 exhibited asymmetric glucose metabolism with severely decreased FDG uptake in the left hemisphere, including the caudate, somatosensorial, and temporal regions. Multiple areas showed an increase in FDG uptake, most notably throughout the right medial hemisphere (Figure S2). They had a 9.5% increase in annualized TMS score, driven mainly by gait and parkinsonism score increases (+37.5%), with predominant rigidity on the right side.

POHD patient 3 exhibited severe reduced glucose metabolism in the somatosensory and temporo-occipital regions and the left striatum, and elevated activity in the frontoparietal regions and the left hippocampus. Their annualized TMS increased by 14.2%, driven mainly by a significant increase in dystonia score (+133.8%); their annualized TFC score decreased by 11.4%.

Discussion

A major unmet need in POHD is establishing a link between biological findings and clinical evidence in vivo.[11] We performed a comprehensive and simultaneous baseline evaluation of the morphologic and metabolic traits in POHD and AOHD brains, and a longitudinal analysis in a subset of patients. Although previous studies have correlated longitudinal striatal volume loss with clinical progression,[12,13] ours is the first to show that both baseline and longitudinal changes, in striatal and nonstriatal regions, may explain clinical differences between POHD and AOHD.

Consistent with a significantly lower striatal volume, striatal glucose metabolism was significantly lower in POHD versus AOHD at baseline, whereas FDG uptake was highly variable in POHD cortical regions, with significantly higher and lower uptake observed, compared to AOHD, depending on region.

In addition to altered glucose metabolism resulting from abnormally low levels of GLUT-1 transporters,[7] protein fragments with long polyQ tracts in *HTT*-Exon-1 lead to the formation of intranuclear inclusions during neurogenesis, affecting mitochondrial function[13] and brain processes such as neurodevelopment, transcriptomic profile, and reduced levels of synaptic and metabolic genes and of cerebral receptors.[14–17]

An unexpected finding was the significantly higher glucose metabolism in the thalamus of POHD patients at baseline compared with AOHD. A thalamic glucose hypermetabolism increase before symptom onset, with a subsequent decrease after phenoconversion, has been described in AOHD as a compensatory process.[18] Our evidence of a still-strong thalamic hypermetabolism in symptomatic POHD patients represents a unique description of the disease and may reflect an inability to compensate for early, severe, and fast striatal volume loss. Further, the presence of specific lateralized regional patterns of altered glucose metabolism in POHD cortex suggests the presence of dysfunctional processes, which may influence the particular features of POHD, including its distinct clinical manifestations and disease progression.[6,12,13]

Our main limitation is the small sample size, especially the longitudinal cohort. However, HD is rare, and pediatric cases are exceptionally rare and progress rapidly, making large-scale recruitment over a limited time frame challenging. Our strict inclusion criteria (≥60 CAG repeats and longitudinal clinical data available from ENROLL-HD) further limited enrolment. Another possible limitation is the difference in the CAP score between POHD and AOHD cohorts. The larger baseline CAP score in POHD might theoretically affect the difference in neuropathological traits with AOHD. However, all clinical evaluations showed a similar clinical condition at baseline in motor, cognitive, and independence items between the 2 cohorts.

Our study still suggests that POHD patients carrying mutations ≥60 CAG repeats have distinct characteristics, with significantly different regional brain volumes and glucose metabolism, versus AOHD patients. In POHD, large and unstable CAG repeats with triplet mosaicism[19] and neuron transcriptional dysregulation changes[20] throughout life[21] may cause dysfunction in different brain regions, affecting clinical variability and severity. The regional and dynamic variability in cortical dysfunction that precedes cortical atrophy is potentially a precursor of clinical manifestation severity in POHD. The hybrid FDG-PET/MRI combines volumetric and metabolic changes in the same individual and may represent a valuable tool for monitoring POHD changes over time.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique.

M.E.C.: 1A, 1B, 1C, 1B, 2A, 2B, 3B
E.T.: 1B, 1C, 3B
P.Z.: 2A, 2B, 3B
G.G.: 1C, 2C, 3B
F.C.: 1B, 1C, 2A, 2B
G.L.C.: 1B, 1C, 2C
U.S.: 1A, 1B, 1C, 2C, 3B
F.S.: 1A, 1B, 1C, 2C, 3A, 3B

Acknowledgments

We are grateful to all families and patients from the LIRH Foundation Network of Huntington Disease patients' associations (eg, LIRH-Puglia, LIRH-Tuscany, LIRH-Sardinia, LIRH Friuli Venezia Giulia, and Noi Huntington) for their continuous support to LIRH research activities. Ferdinando Squitieri is the CSO of the Italian League for Huntington (LIRH) Foundation. We also thank Dr. Abigail Woollard, a professional medical writer funded by the LIRH Foundation, for providing editorial revisions to the draft manuscript. LIRH Foundation received funding from the Cure Huntington's Disease Initiative Foundation for collecting patient data and samples in the ENROLL-HD platform. Open access funding provided by BIBLIOSAN.

Disclosures

Ethical Compliance Statement: RAREST-JHD study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local Institutional Ethical Committee of IRCCS Casa Sollievo della Sofferenza on April 9, 2018 (Prot. N52/CE). All patients provided written informed consent prior to enrolment into the study. All ENROLL-HD sites were required to obtain and maintain local ethics committee approvals. Participants must have signed informed consent forms for their data to be included in the datasets. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: This study was financially supported by LIRH Foundation (funds from "5X1000" of taxes to Giulia Giancaterino and Ferdinando Squitieri) and by the Italian Ministry of Health (funds from Ricerca Finalizzata [RF-2016-02364123] to Umberto Sabatini and Ferdinando Squitieri). All authors declare that there are no conflicts of interest for this work.

Financial Disclosures for the Previous 12 Months: All authors report no financial disclosures for this work. ■

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Supporting Information

Supporting information may be found in the online version of this article.

Figure S1. Annualized percentage rate of morphological changes in the AOHD cohort (averaged from 6 patients) and individual POHD patients (analyzed individually due to a small n number and a high clinical and metabolic variability). From left to right: left lateral, left medial, right medial, and right lateral views of the cortex; then left lateral, left medial, right medial, and right lateral views of subcortical structures. Color bars show annualized percentage changes in morphology (increases in red, decreases in blue). AOHD, adult-onset Huntington's disease; POHD, pediatric-onset Huntington's disease.

Figure S2. Annualized percentage rate of changes in glucose uptake in the AOHD cohort (averaged from 6 patients) and individual POHD patients (analyzed individually due to a small n number and a high clinical and metabolic variability). From left to right: left lateral, left medial, right medial, and right lateral views of the cortex; then left lateral, left medial, right medial, and right lateral views of subcortical structures. Color bars show annualized percentage changes in glucose metabolism (increases in red, decreases in blue).

Table S1. Demographic and clinical characteristics of the longitudinal cohort (n = 9). Data are reported as median and range. Higher scores on the TMS (Total Motor Score) indicate more severe motor impairment, whereas higher sores for TFC (Total Functional Capacity), IS (Independence Scale), MMSE (Mini-Mental State Examination), SDMT (Symbol Digit Modality Test), SVF (Semantic Verbal Fluency), SCN (Stroop Color Naming), and SWR (Stroop Word Reading) indicate better functional capacity, independence, or cognitive performance.

Data S1. Supporting information.