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Positive effect of immunomodulatory therapies on disease progression in Huntington's disease? Data from a real-world cohort

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Abstract

Background: The role of neuroinflammation and autoimmune processes in neurodegenerative diseases is not fully understood. Activation of microglia with expression of proinflammatory cytokines supports the hypothesis that immune processes may play an important role in the pathophysiology of Huntington's disease (HD) and thus, immunomodulating therapies might have potential neuroprotective properties. Until now, no disease-modifying therapy (DMT) is available for HD.

Objective: The aim of this research was to characterize a cohort of patients suffering from both HD and autoimmune demyelinating diseases of the central nervous system (classified as G35-37 in ICD-10; ADD-CNS) in comparison to HD cases without ADD-CNS. In particular, we were interested to investigate potential modulating effects on disease manifestation and progression of HD over time of prescribed immunomodulating medications (DMT).

Methods: We analyzed the course of HD regarding motoric, functional, and cognitive aspects, using longitudinal data of up to 2 years from the worldwide registry study ENROLL-HD. Additional cross-sectional data in the largest cohort worldwide of HD patients was analyzed using demographic and molecular genetic parameters. Data were analyzed using analysis of variance (ANOVA) for cross-sectional and repeated-measures ANOVA for longitudinal parameters in IBM SPSS Statistics V.27.

Results: Within the ENROLL-HD database, we investigated $N = 21{,}116$ participants and identified $n = 60$ participants suffering from ADD-CNS. Molecular, genetic, and demographic data did not differ between groups. The subgroup of $n = 32$ participants with motor-manifest HD revealed better cognitive performance in five out of eight cognitive tests at baseline with less progression over time in two tests (all $p < 0.05$). Differentiation between DMT-treated and untreated patients revealed better cognitive and motor performance in the DMT group; those patients, however, tended to be younger. Pre-manifest HD patients simultaneously diagnosed with ADD-CNS ($n = 12$) showed lower functional scores and more decline over time when compared with other pre-manifest HD ($p < 0.05$).

Conclusion: Patients suffering from motor-manifest HD and simultaneously from ADD-CNS have better cognitive capacities compared with other motor-manifest HD patients. Moreover, DMTs might have beneficial effects on progression of neurodegeneration including the motor phenotype. However, this effect might have been biased by younger age in DMT-treated patients. Pre-manifest HD patients showed more functional impairment as expected due to their additional ADD-CNS disease.

Keywords: autoimmune demyelinating diseases, ENROLL-HD, Huntington's disease, immunomodulation, multiple sclerosis, neuroinflammation

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Introduction

Suffering from neurodegenerative Huntington's disease (HD) is accompanied with manifold heterogeneous motoric, cognitive, and psychiatric symptoms.[1–3] Although the distinct cause of disease is known with a Cytosine-Adenine-Guanine (CAG)-trinucleotide repeat expansion in the huntingtin gene (*HTT*) encoding for mutant huntingtin protein (*mHTT*) associated with toxic effects at the molecular level, exact pathomechanisms remain to be elucidated.[1] There is evidence that molecular changes and pathophysiology in HD is accompanied by neuroinflammation due to an influence of the innate and adaptive immune system with activation of microglia and expression of proinflammatory cytokines in the striatum accelerating neurodegenerative processes starting in pre-manifest stages of the disease already.[4–7] Elevation of pro-inflammatory cytokines such as interleukin (IL)-6, IL-7, and others in animal models and patients suggests inflammatory mechanisms as part of the pathophysiology in HD. [5,8–10] It remains uncertain whether neuroinflammation embosses neurodegenerative disease progression or is the result of a reactive process.[4] Inflammation following neuronal damage is seen as double-edged sword since chronic inflammatory processes can fuel neurodegeneration, as seen in progressive multiple sclerosis,[11] but also elicit regenerative and reparative processes as 'protective autoimmunity' mediated through anti-inflammatory cytokines produced by activated T cells.[12–15] A better understanding of these neuroimmune interactions is necessary in order to develop effective therapies in neuroimmunological and neurodegenerative diseases.[12] Besides HD, the involvement of neuroinflammatory processes is also discussed in other neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), amyotrophic lateral sclerosis, and spinocerebellar ataxia.[12] Thus, findings from HD might also be relevant for other neurodegenerative diseases.

Neurodegenerative processes like in HD, AD, or PD–as neurodegenerative diseases–also occur in neuroimmunological diseases such as multiple sclerosis (MS), especially during the progressive phase of the disease,[12,16] supporting the concept of shared mechanisms in primary neurodegenerative and neuroinflammatory diseases. One example is the accumulation of iron during both progressive multiple sclerosis[11,17] and neurodegenerative diseases such as HD and the impairment of transport proteins as a potential target for treatment.[18–21]

Manifold therapeutic approaches have used immunotherapies and modulating strategies against immune activation as promising targets for the treatment of neurodegeneration in preclinical HD models.[22–26] While Laquinimod treatment leads to improved motor function and improved histopathological findings only, FTY720 (fingolimod), fumaric acid, and glatiramer acetate (GA) not only improved motor function but also prolonged survival in HD animal models.[23,26] Laquinimod so far is the only substance investigated in a big clinical trial in human (LEGATO-HD, NCT02215616). However, the study failed to reach the primary endpoint of a change of the total motor score (TMS) in the Unified Huntington's Disease Rating Scale (UHDRS) scale after 52-week treatment, while there was a reduction in brain atrophy as a secondary outcome measure.[23,27,28] Hence, until now only animal models have shown improvements with regard to immunomodulatory therapies in HD and there is still an urgent need to get a better understanding of underlying neuroinflammatory pathways in neurogenerative disease, especially with a translational focus.

Promising therapeutic approaches like antisense or small molecules for huntingtin reduction or gene-based therapies have been made during the last decade, but there is still no evidence for disease-modifying therapies (DMTs) or beneficial immunotherapies in HD, yet.[29–31]

The aim of this research was to characterize a cohort of patients suffering simultaneously from HD and from autoimmune demyelinating disease of the central nervous system (classified as G35-37 in ICD-10; ADD-CNS) in a large real-world cohort for the first time. We were interested to identify prescribed immunomodulating pharmacotherapies in groups to analyze potentially modulating effects on disease manifestation and progression of HD.

Methods

ENROLL-HD database

We investigated HD participants and participants suffering from ADD-CNS within the global cohort of the ENROLL-HD registry study.

Enroll-HD is a global clinical research platform designed to facilitate clinical research in HD. Core datasets are collected annually from all research participants as part of this global multicenter longitudinal observational study. Data are monitored for quality and accuracy using a risk-based monitoring approach. All sites are required to obtain and maintain local ethical approval. We investigated the periodic dataset five (PDS-5) as previously described.[30,32] Ethics approval was obtained by the local ethics committee of Ruhr-University Bochum (No. 4941-14).

Participants were categorized into the groups pre-manifest HD suffering from ADD-CNS, and manifest HD suffering from ADD-CNS. In addition, two control groups were identified for each category having pre-manifest HD without ADD-CNS and manifest HD without ADD-CNS. We first compared baseline data of study entry in a cross-sectional approach. As inclusion criteria for manifest HD group, all included participants had a diagnostic confidence level (DCL) of 4 [unequivocal signs of clinical manifest HD (>99% confidence)], a total motor score (TMS) >5, and a genetically confirmed report with ⩾36 CAG repeats in the Huntingtin gene (*HTT*). Longitudinal data with annual (±3 months) follow-up visits of up to two more years were analyzed to compare disease manifestation and progression over time.

Fundamental demographic and molecular genetic parameters were assessed analyzing CAG-repeat lengths, age, CAP-scores,[33] sex, educational level, age at HD diagnosis, and age at onset of symptoms reported by the patient, family, and rater between groups. Motoric parameters were analyzed using the UHDRS–Total motor score. Cognitive performance was evaluated with the ENROLL-HD test battery including eight cognitive tests: symbol digit modality test (SDMT), verbal fluency test (category; Verfct), verbal fluency test (Letters; Verflt), Stroop color naming (SCN), Stroop word reading (SWR), Stroop interference test (SIT), Mini-Mental State Examination (MMSE), and Trailmaking test (Trla). Functionality was analyzed with the UHDRS-Total functional capacity (TFC), described additionally with TFC stages and the Independence Scale (IS).

Statistical analyses

Group means and standard deviation for cross-sectional data were assessed using analysis of variance (ANOVA) for disease manifestation at baseline visit in IBM SPSS Statistics V.27. Homogeneity of variances was asserted using Levene's test. Detecting unequal variances, values were reported with the Welch's test. Dependent variables were tested for normal distribution using the Kolmogorov–Smirnov test (data not shown). Parametric test procedures were used as part of the study design with ANOVA analysis. Chi-square tests were used for the analysis of categorical variables. We performed multiple ANOVA analyses between groups to compare participants from ADD-CNS/HD-group with control ADD-CNS-category. Afterward, repeated-measures ANOVA were conducted to determine differences between participant categories with longitudinal data over 2 years. Adjustment for multiple testing was applied using Bonferroni corrections.

To assure correctness of obtained results, we performed a propensity-score matching using the variables age, CAG repeat length, sex, and education (ISCED) and matched ADD-CNS with immunomodulating therapies 1:3 participants to manifest. Same analysis was performed for pre-manifest and all manifest HD patients with autoimmune demyelination compared with control-matched subjects. We analyzed motoric, functional, and cognitive performances using *t*-tests.

Results

Participants and data analyses

Within Enroll-HD periodic dataset five, we analyzed data of $N = 21{,}116$ participants. In total, we identified $n = 60$ participants in the database suffering from ADD-CNS, whereby $n = 56$ participants were diagnosed with multiple sclerosis (G35). Three participants were classified suffering from 'demyelinating disease of central nervous system, unspecified' (G 37.9) and $n = 1$ from 'acute transverse myelitis in demyelinating disease of central nervous system' (G37.3). The participant suffering from G37.9 was diagnosed with the additional disease from −1693 to −232 days (1461 days in total) prior to baseline assessment and categorized as a manifest HD patient. In total, $n = 32$ out of these $n = 60$ participants were suffering additionally from motor-manifest HD. Twelve were classified as HD gene carriers with a pre-motor manifest status and $n = 16$ with a

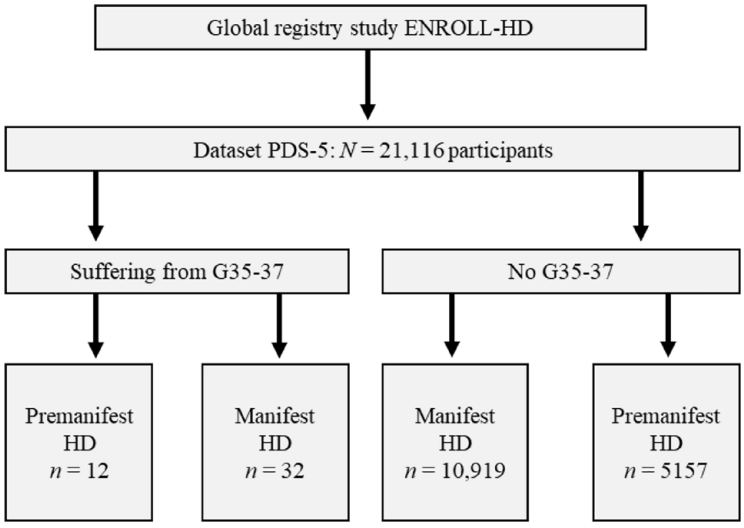

Figure 1. Workflow for assessing participants in ENROLL-HD dataset suffering from HD, G35-37 (ADD-CNS), and controls.
HD, Huntington's disease; *n*/*N*, number; PDS-5, periodic dataset 5.

negative HD phenotype or included as family controls without suffering from HD (excluded from further analysis). Therewith, the majority of the HD group suffering from G35-37 were manifest HD patients.

For pre-manifest and manifest HD, control groups without ADD-CNS were identified, revealing $n = 10{,}919$ participants as motor-manifest HD and $n = 5157$ as pre-manifest HD participants in the global registry study (Figure 1).

Transformed into days relative prior to baseline assessment, whole group of $n = 60$ ADD-CNS participants suffered in average since 3402 days (SD ± 3371) from ADD-CNS. Differentiated into subgroups, revealed manifest HD ADD-CNS ($n = 32$) suffered in average since 3525 days (SD ± 3375) and pre-manifest HD ADD-CNS ($n = 12$) since 3432 days (SD ± 3697) from ADD-CNS.

Manifest HD suffering additionally from ADD-CNS revealed better cognition if compared with other motor-manifest HD patients

Assessing cross-sectional data between groups revealed no differences in fundamental demographic, molecular genetic, onset-data, motoric, functional, and psychiatric performance between manifest HD patients suffering from ADD-CNS and other manifest HD patients within the ENROLL-HD database. The calculated CAP-Score revealed a significantly lower level in manifest HD patients with autoimmune demyelination compared with those without the additional disease.

First, we analyzed TFC subscales of the UHDRS functional assessment defined as: stage 1 (TFC 11–13), stage 2 (TFC 7–10), stage 3 (TFC 3–6), stage 4 (TFC 1–2), and stage 5 (TFC 0) between groups.[34,35] In total, $n = 12$ subjects out of our ADD-CNS group were classified as stage 1 (manifest HD without ADD-CNS: $n = 3684$), $n = 12$ as stage 2 (manifest HD without ADD-CNS: $n = 3750$), $n = 3$ as stage 3 (manifest HD without ADD-CNS: $n = 2332$), $n = 5$ as stage 4 (manifest HD without ADD-CNS: $n = 809$), and none as stage 5, respectively (manifest HD without ADD-CNS: $n = 312$). Thus, the majority of all patients were early stage HD patients in both groups.

The cognitive test battery determined that manifest HD patients with ADD-CNS performed significantly better in the Symbol digit modality, the Verbal fluency (category), the Stroop color naming, the Stroop interference, and the Verbal Fluency test (Letters) during baseline assessment (all $p < 0.050$; Table 1). The performed propensity score 1:3 matching for manifest HD suffering from ADD-CNS tested robustness of the observed effects and confirmed that analyzed ADD-CNS patients have better cognitive performances within five out of eight cognitive tests (see Appendix 1).

Better cognition in HD patients suffering from ADD-CNS compared with other manifest HD patients over three consecutive study visits

Having established cross-sectional baseline data of motor-manifest HD participants, we investigated three consecutive Enroll-HD visits per patient to analyze whether the differences identified at baseline persists when data of more than one study visit were combined as repeated measures. Longitudinally, no differences were observed between motor-manifest HD patients additionally suffering from ADD-CNS and other HD participants in the database regarding motoric and functional assessments over a time period of two more years.

Regarding cognitive performance, there remained a difference in the performance in Stroop color

Table 1. Baseline data of manifest HD with ADD-CNS and HD patients at baseline visit.

Domain/variable	Manifest HD suffering from ADD-CNS (*n* = 32)	Manifest HD (*n* = 10,919)	Levene's test	*F*	*p*	Part. eta²
Age (years); M (SD)	49.3 (10.3)	52.9 (12.8)	0.138	2.630	0.105	0.000
CAG high (SD)	43.5 (2.9)	44.0 (3.9) (*n* = 10,887)	0.454	0.608	0.436	0.000
CAP-Score (SD)	465.2 (97.2)	511.1 (99.4)	0.939	6.811	0.009	0.001
Sex (f/m) (%f)	21/11 (65.6)	5610/5309 (51.4)	NA	2.643	0.114	0.000
Hddiagn (years) (SD)	46.5 (10.3) (*n* = 27)	49.0 (12.7) (*n* = 10,575)	0.368	0.869	0.351	0.000
Sxrater (years) (SD)	44.7 (9.2) (*n* = 28)	46.3 (12.2) (*n* = 10,687)	0.888	0.383	0.536	0.000
Sxsubj (years) (SD)	44.7 (9.6) (*n* = 27)	46.4 (12.7) (*n* = 10,089)	0.099	0.430	0.512	0.000
Sxfam (years) (SD)	43.5 (9.5) (*n* = 24)	45.7 (12.6) (*n* = 9882)	0.091	0.632	0.427	0.000
ISCED (SD)	3.4 (1.3)	3.4 (1.2) (*n* = 10,817)	0.945	0.004	0.948	0.000
Motoric UHDRS TMS; M (SD)[a]	32.1 (24.3)	37.8 (21.5) (*n* = 10,781)	0.876	2.221	0.136	0.000
TFC; M (SD)[b]	8.6 (3.9)	8.2 (3.7) (*n* = 10,853)	0.640	0.380	0.538	0.000
IS; M (SD)[b]	76.1 (20.2)	77.0 (18.9) (*n* = 10,852)	0.882	0.058	0.810	0.000
SDMT; M (SD)[b]	**28.8 (13.3) (*n* = 29)**	**23.0 (2.9) (*n* = 9937)**	**0.530**	**5.848**	**0.016**	**0.001**
Verfct; M (SD)[b]	**14.3 (8.0)**	**12.0 (5.8) (*n* = 10,475)**	**0.149**	**5.034**	**0.025**	**0.000**
SCNT; M (SD)[b]	**48.9 (20.4) (*n* = 31)**	**41.7 (18.0) (*n* = 10,330)**	**0.999**	**5.044**	**0.025**	**0.000**
SWRT; M (SD)[b]	62.5 (25.3) (*n* = 31)	55.5 (23.6) (*n* = 10,281)	0.584	2.807	0.094	0.000
SIT; M (SD)[b]	**28.2 (13.5) (*n* = 30)**	**23.4 (11.6) (*n* = 8893)**	**0.738**	**5.120**	**0.024**	**0.001**
Verflt; M (SD)[b]	**27.1 (13.2) (*n* = 24)**	**21.0 (13.0) (*n* = 7754)**	**0.947**	**5.305**	**0.021**	**0.001**
Trla; M (SD)[a]	56.0 (49.1) (*n* = 21)	72.9 (53.0) (*n* = 7204)	0.337	2.134	0.144	0.000
MMSE; M (SD)[b]	26.3 (4.7) (*n* = 15)	24.8 (4.5) (*n* = 6819)	0.490	1.623	0.203	0.000

ADD-CNS, autoimmune demyelinating disease of the central nervous system; CAG, Cytosine-Adenine-Guanine repeat length; CAP-Score, CAG-Age Product Index; HD, Huntington's disease; Hddiagn, Huntington's disease diagnosed; IS, Independence scale; ISCED, Educational level; MMSE, Mini-Mental State Examination; SCNT, Stroop color naming test; SD, standard deviation; SDMT, symbol digit modality test; SIT, Stroop interference test; Sxfam, families estimate of symptom onset; Sxrater, rater's estimate of symptom onset; Sxsubj, subject estimate of symptom onset; SWRT, Stroop word reading test; TFC, total functional capacity; TMS, total motor score; Trla, Trailmaking A test; UHDRS, Unified Huntington's Disease Rating Scale; Verfct, verbal fluency test (category); Verflt, verbal fluency test (Letters). Bold values: significant differences between groups.
Assessing cross-sectional data using univariate analysis of variance between groups revealed manifest HD patients suffering additional from ADD-CNS showing better cognitive performance in five cognitive testing if compared with other motor-manifest HD participants.
[a]Higher scores = more impairment.
[b]Higher scores = better performance.

naming, Stroop interference, and verbal fluency test (Letters) over time (all $p < 0.050$; Table 2).

Baseline data of pre-manifest HD with ADD-CNS versus pre-manifest other HD patients

Regarding pre-manifest HD participants suffering additionally from ADD-CNS, we identified significantly more female participants and less functionality capacity depicted in the Independence Scale (all $p < 0.050$) when compared with other pre-manifest HD patients. Regarding all other motoric, functional, cognitive, and psychiatric parameters, no further significant group differences were identified (Table 3). To test robustness of observed effects, we performed a 1:3 propensity-score matching for pre-manifest HD suffering from ADD-CNS and analyzed motoric, functional, and cognitive disease. This analysis confirmed no differences between pre-manifest ADD-CNS patients in cognitive and motoric capacities. Although the IS tended to be lower in ADD-CNS patients, no significant differences were confirmed (see Appendix 2).

Longitudinal repeated-measures analysis of variance in pre-manifest groups revealed no statistically significant differences between groups of pre-manifest HD participants with ADD-CNS ($n = 5$) and other pre-manifest HD ($n = 2033$) regarding baseline and two more follow-up visits, except from Independence scale determining more mean decline over time in pre-manifest HD patients ($F = 8.231, p = 0.004$, partial $\text{eta}^2 = 0.004$).

Pharmacological treatment within manifest HD patients suffering from ADD-CNS

Within the ENROLL-HD database, pharmacotherapies with indications are available for each individual participant besides comorbidities and non-pharmacological treatments. Date values are referring to visit dates and reflect the number of days intake before baseline of study entry or follow-up visits. The data file collection of pharmacotherapies implements the drug name, ingredients, the total daily dose/unit, frequency, and route of intake.

Immunomodulating and other therapies prescribed because of ADD-CNS were analyzed within the manifest HD group suffering from ADD-CNS ($n = 32$). We therefore analyzed intake and duration of DMTs within the cohort prior to baseline (Figure 2).

$N = 11/32$ participants in the manifest HD with ADD-CNS group received additionally other medications prescribed because of ADD-CNS such as baclofen, methionine, or amantadine (not shown).

As an additional explorative approach, subgroups of manifest HD patients suffering from ADD-CNS ($n = 32$) were analyzed, comparing participants out of this group with distinct ($n = 13$) and with no known DMT ($n = 19$) to motor manifest other HD participants ($n = 10{,}919$) (Tables 4 and 5). With regard to age at HD diagnosis, patients with immunomodulating therapies [mean age, 44.5 (SD, 8.9)] revealed no significant differences compared with other manifest HD patients [mean age, 48.8 (SD, 12.9); $F = 1.216$, $p = 0.270$, partial $\text{eta}^2 = 0.000$]. In addition, no significant differences were observed for disease duration between immunomodulated HD ADD-CNS [5.5 years (SD, 8.9)] and manifest HD [9.5 years (SD, 14.0); $F = 2.433$, $p = 0.119$, partial $\text{eta}^2 = 0.000$]. To test robustness of observed effects, we performed a 1:3 propensity-score matching using the variables age, CAG repeat length, sex, and education for manifest HD suffering from ADD-CNS with immunomodulating therapies and analyzed motoric, functional, and cognitive disease. Since for one patient no information about the educational level was available, no corresponding propensity score could be calculated so that this patient had to be excluded from the further analysis. The analysis of all other $n = 12$ subjects confirmed that ADD-CNS patients have better cognitive performances within five out of eight cognitive tests (see Appendix 3).

Discussion

Until now it remains unsolved how neurodegeneration and neuroinflammation influence themselves in chronic – either primary or secondary neurodegenerative conditions. This conundrum has huge implications for affected patients, since specific therapeutic interventions could be implemented to target especially inflammatory processes, potentially reducing degeneration. To investigate this question, we took advantage of a huge database of patients suffering from HD as primary neurodegenerative condition, afflicted

Table 2. Analysis of motor, function and cognitive parameters between groups upon three consecutive Enroll-HD study visits.

Domain/ variable	Manifest HD suffering from ADD-CNS (*n* = 15)				Manifest HD (*n* = 4382)				Inter-subject analysis		
	BL	FU 1	FU 2	Δ FU2-BL per group	BL	FU1	FU2	Δ FU2-BL per group	*F*	*p*	Part. eta²
TMS; M (SD)[a]	29.0 (26.3)	35.5 (27.9)	36.5 (28.7)	7.5	35.9 (20.7) (*n* = 4277)	39.5 (21.7)	43.2 (23.0)	7.3	0.818	0.603	0.002
TFC; M (SD)[b]	8.6 (3.8)	8.2 (4.1)	8.2 (4.1)	0.4	8.4 (3.5) (*n* = 4377)	7.7 (3.6)	7.1 (3.7)	1.3	0.176	0.675	0.000
IS; M (SD)[b]	76.0 (23.2)	71.7 (23.7)	75.0 (23.1)	1.0	78.0 (17.4)	74.5 (18.4)	71.2 (19.6)	6.8	0.006	0.940	0.000
SDMT; M (SD)[b]	30.1 (14.4) (*n* = 14)	29.8 (16.6)	27.1 (14.2)	3.0	26.1 (12.3) (*n* = 3548)	24.7 (12.6)	23.0 (12.9)	3.1	1.819	0.178	0.000
Verfct; M (SD)[b]	15.6 (9.3) (*n* = 14)	14.4 (8.3)	14.4 (7.5)	1.2	13.0 (5.6) (*n* = 3952)	12.3 (5.8)	11.5 (5.9)	1.5	3.152	0.076	0.001
SCNT; M (SD)[b]	**54.4 (22.9) (*n* = 14)**	**48.4 (22.0)**	**50.0 (21.5)**	**4.4**	**44.7 (16.5) (*n* = 3844)**	**42.4 (16.8)**	**39.8 (17.2)**	**4.9**	**4.068**	**0.044**	**0.001**
SWRT; M (SD)[b]	67.8 (26.0) (*n* = 14)	62.0 (25.4)	64.4 (25.3)	3.4	59.4 (21.4) (*n* = 3802)	55.9 (22.0)	52.3 (22.6)	7.1	2.528	0.112	0.001
SIT; M (SD)[b]	**34.3 (13.4) (*n* = 13)**	**32.5 (14.5)**	**29.7 (13.0)**	**4.6**	**25.9 (11.1) (*n* = 3041)**	**24.8 (11.2)**	**23.3 (11.4)**	**2.6**	**6.629**	**0.010**	**0.002**
Verflt; M (SD)[b]	**34.4 (12.5) (*n* = 9)**	**31.6 (13.8)**	**37.0 (13.4)**	**+2.6**	**23.5 (12.9) (*n* = 2582)**	**23.1 (13.3)**	**22.0 (13.9)**	**1.5**	**7.270**	**0.007**	**0.003**
Trla; M (SD)[a]	40.4 (18.4) (*n* = 8)	43.5 (25.1)	43.6 (17.7)	3.2	61.7 (40.1) (*n* = 2372)	64.9 (44.2)	70.9 (50.7)	9.2	2.500	0.114	0.001
MMSE; M (SD)[b]	29.0 (1.7) (*n* = 3)	28.7 (1.5)	28.0 (2.0)	1.0	25.7 (3.6) (*n* = 2231)	25.4 (4.0)	24.8 (4.5)	0.9	2.244	0.134	0.001

ADD-CNS, autoimmune demyelinating disease of the central nervous system; BL, Baseline visit; FU, Follow up visit; HD, Huntington's disease; IS, Independence scale; MMSE, Mini-Mental State Examination; SCNT, Stroop color naming test; SDMT, Symbol digit modality test; SIT, Stroop interference test; SWRT, Stroop word reading test; TFC, total functional capacity; TMS, total motor score; Trla, Trailmaking A test; Verfct, verbal fluency test (Category); Verflt, verbal fluency test (Letters). Bold values significant differences between groups.
Data were analyzed using repeated-measures analysis of variance between groups at baseline and two more follow-up visits. Data depicted as mean performance levels (standard deviation) in groups and inter-subject effects.
[a]Higher scores = more impairment.
[b]Higher scores = better performance.

also by a demyelinating condition, mostly multiple sclerosis. We identified a cohort of $n = 21{,}116$ participants within the ENROLL-HD dataset and $n = 32$ manifest HD patients suffering also from ADD-CNS. With an estimated prevalence of 250,000 patients suffering from MS in Germany and approximately 2.5 million individuals worldwide, we previously did not expect high number of patients suffering from ADD-CNS and HD.[36,37] Remarkably, $n = 32$ out of $n = 10{,}919$ motor-manifest HD participants (0.29%) additionally were suffering from ADD-CNS within the database. The latter group revealed better cognitive performance at baseline and less decrease in more longitudinal cognitive capacities over time, although molecular genetic, demographic, and onset parameters as fundamental disease status revealed no differences between groups. Hence, one can suggest that described differences might be due to the additional ADD-CNS diagnosis. However, to prove this hypothesis, further research with especially larger cohorts is necessary. Although patients were suffering from the two manifest serious diseases, remarkably no increased cognitive, motoric, functional, or psychiatric symptoms were observed.

Table 3. Baseline data of pre-manifest HD with ADD-CNS and pre-manifest HD patients.

Domain/variable	Pre-manifest HD suffering from ADD-CNS (*n* = 12)	Pre-manifest HD (*n* = 5157)	Levene's test	*F*	*p*	Part. eta²
Age (years); M (SD)	43.7 (9.8)	39.8 (12.1)	0.211	1.210	0.271	0.000
CAG high (SD)	41.0 (1.3)	42.4 (2.8)	0.054	2.899	0.089	0.001
CAP-Score (SD)	315.9 (73.0)	329.0 (92.0)	0.451	0.243	0.622	0.000
Sex (f/m) (%f)	**11/1 (91.7)**	**3085/2072 (59.8)**	**NA**	**5.054**	**0.035**	**0.000**
ISCED (SD)	4.1 (1.2)	4.0 (1.1) (*n* = 5141)	0.981	0.151	0.697	0.000
Motoric UHDRS TMS; M (SD)[a]	3.7 (5.3)	3.0 (4.5) (*n* = 5135)	0.523	0.239	0.625	0.000
TFC; M (SD)[b]	12.5 (0.9)	12.7 (0.9) (*n* = 5140)	0.283	0.669	0.413	0.000
IS; M (SD)[b]	**96.7 (6.1)**	**99.0 (3.8) (*n* = 5151)**	**0.034**	**4.478**	**0.034**	**0.001**
SDMT; M (SD)[b]	49.0 (15.0)	49.3 (12.1) (*n* = 5123)	0.239	0.008	0.931	0.000
Verfct; M (SD)[b]	23.0 (6.7)	21.2 (5.7) (*n* = 5117)	0.510	1.219	0.270	0.000
SCNT; M (SD)[b]	65.6 (19.2)	72.4 (14.8) (*n* = 5110)	0.254	2.499	0.114	0.000
SWRT; M (SD)[b]	85.6 (27.0)	92.8 (18.4) (*n* = 5114)	0.019	1.811	0.178	0.000
SIT; M (SD)[b]	41.2 (11.8)	43.0 (11.3) (*n* = 4833)	0.787	0.314	0.575	0.000
Verflt; M (SD)[b]	39.2 (14.1) (*n* = 11)	39.3 (12.8) (*n* = 4247)	0.840	0.001	0.970	0.000
Trla; M (SD)[a]	30.0 (11.1) (*n* = 11)	28.1 (13.5) (*n* = 4246)	0.758	0.225	0.635	0.000
MMSE; M (SD)[b]	28.1 (2.3) (*n* = 7)	28.6 (4.5) (*n* = 3645)	0.184	0.629	0.428	0.000

ADD-CNS, autoimmune demyelinating disease of the central nervous system; CAG, Cytosine-Adenine-Guanine repeat length; CAP-Score, CAG-Age Product-Index; HD, Huntington's disease; Hddiagn, Huntington's disease diagnosed; IS, Independence scale; ISCED, Educational level; MMSE, Mini-Mental State Examination; SCNT, Stroop color naming test; SDMT, Symbol digit modality test; SIT, Stroop interference test; Sxfam, families estimate of symptom onset; Sxrater, rater's estimate of symptom onset; Sxsubj, subject estimate of symptom onset; SWRT, Stroop word reading test; TFC, total functional capacity; TMS, total motor score; Trla, Trailmaking A test; UHDRS, Unified Huntington's Disease Rating Scale; Verfct, verbal fluency test (category); Verflt, verbal fluency test (Letters).
Bold values: significant differences between groups.
Cross-sectional data using univariate analysis of variance between pre-manifest HD participants' additionally suffering from ADD-CNS and other pre-manifest HD participants.
[a]Higher scores = more impairment.
[b]Higher scores = better performance.

One possible explanation for better cognitive performance in the HD-ADD-CNS group might have been the use of DMTs.[38] Several DMTs have shown positive effects investigated in preclinical or HD animal models leading to improved motor function, histopathological findings and in most cases also prolonged survival such as GA[24] or laquinimod.[23,25,26] Thus, there is good evidence for potential neuroprotective properties of immunomodulating therapies coming from HD

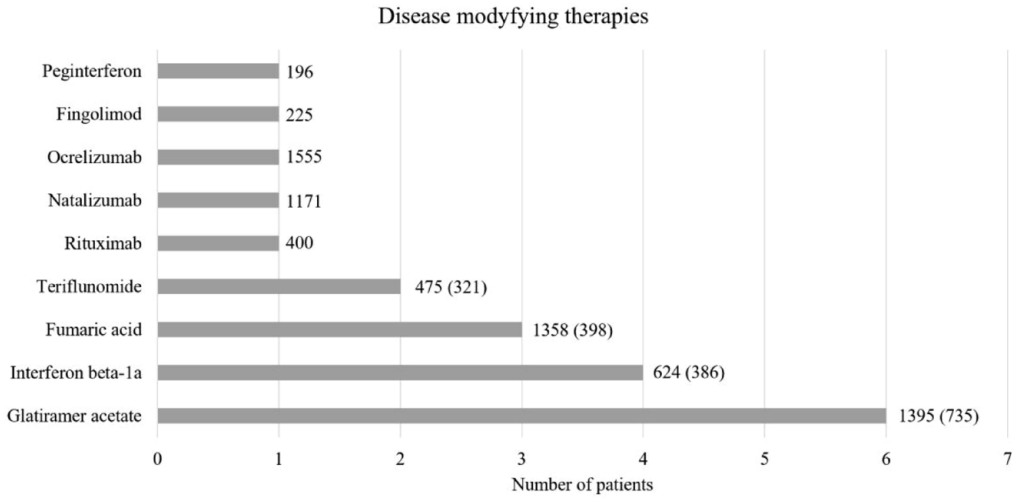

Figure 2. DMTs in the HD with ADD-CNS group prior to baseline assessment. Duration of treatment given in days as mean (standard deviation).

animal models. Although the LEGATO-HD trial conducted in HD failed to reach primary endpoints of motoric benefits, participants treated with laquinimod showed less brain atrophy in comparison to placebo.[27]

We identified $n=13$ participants treated with DMTs and differentiated $n=19$ participants without named DMT therapy in the dataset. DMT-treated patients showed better cognitive performances, confirmed within an explorative propensity score analysis with subsequent testing for cognitive parameters and even motoric performances when compared with other motor-manifest HD. We cannot exclude that this effect might, although not significant, be mediated by younger age, since patients in the DMT group were 6.7 years younger than untreated patients, which could be the explanation for both better motoric and cognitive performance. In light of the HD diagnosis, a significant better motoric performance in this group indeed rather suggests that the effect might have been mediated by age. To test robustness of observed effects, we performed a propensity-score matching controlling for age, CAG repeat length, sex, and education and confirmed that ADD-CNS HD patients have better cognitive capacities in five out of eight tests. These findings support the hypothesis of beneficial effects within the immunomodulated group. However, further underlying effects such as genetic modifiers which have been investigated in genome-wide association studies affecting cognitive domains in HD need to be discussed as potential influencer of disease manifestation.[39,40] Robustness of observed effects was additionally tested for pre-manifest and all manifest ADD-CNS HD patients using the propensity-score matching approach, supporting findings from our former analysis.

With $n=6$ patients, the DMT GA was used most frequently in the overall cohort. GA is licensed as a first-line therapeutic for relapsing-remitting multiple sclerosis and clinically isolated syndrome. GA elicits a broad range of mechanisms[41] such as a switch from Th1-cells to GA-specific Th-2 lymphocytes, resulting in higher levels of neurotrophic factors as a neuroprotective mechanism induced by GA.[42,43] GA has also been studied in different HD models, having shown neuroprotective effects *in vitro* and *in vivo* due to immunomodulating effects on microglia and increased active brain-derived neurotrophic factor (BDNF) in astrocytes.[24] GA treated mice showed a delayed onset of HD and reduced behavioral symptoms, accompanied by increased levels of BDNF and reduced levels of cytokines IL-4 and IL-12, postulating GA as a useful therapeutic target for clinical treatment of HD.[44,45] Moreover, animal models of depression showed beneficial effects of GA on psychiatric behaviors and on cognitive dysfunction even without increased BDNF levels, postulating other unknown mechanisms of the GA-metabolism resulting in positive effects on cognition.[46]

Those data combined suggests the hypothesis that GA might have induced immunomodulating and

Table 4. ADD-CNS with immunomodulating therapies *versus* control at baseline visit.

Domain/variable	Manifest HD suffering from ADD-CNS group with immunomodulating therapies (*n* = 13)	Manifest HD (*n* = 10,919)	*F*	*p*	Part. eta²
Age (years); M (SD)	46.2 (8.9)	52.9 (12.8)	3.587	0.058	0.000
CAG high (SD)	44.2 (2.8)	44.0 (3.9) (*n* = 10,887)	0.041	0.839	0.000
CAP-Score (SD)	469.9 (73.8)	507.6 (116.2)	1.369	0.242	0.000
Motoric UHDRS TMS; M (SD)[a]	**21.4 (14.9)**	**37.8 (21.5) (*n* = 10,781)**	**7.463**	**0.006**	**0.000**
TFC; M (SD)[b]	9.7 (4.4)	8.2 (3.7) (*n* = 10,853)	2.108	0.147	0.000
IS; M (SD)[b]	83.5 (12.8)	77.0 (18.9) (n = 10,852)	1.549	0.213	0.000
SDMT; M (SD)[b]	**31.6 (9.8)**	**23.0 (2.9) (*n* = 9937)**	**5.853**	**0.016**	**0.000**
Verfct; M (SD)[b]	14.7 (8.4)	12.0 (5.8) (*n* = 10,475)	2.715	0.099	0.000
SCNT; M (SD)[b]	**51.7 (12.5)**	**41.7 (18.0) (*n* = 10,330)**	**4.097**	**0.043**	**0.000**
SWRT; M (SD)[b]	**68.6 (18.8)**	**55.5 (23.6) (*n* = 10,281)**	**4.053**	**0.044**	**0.000**
SIT; M (SD)[b]	**30.3 (11.1)**	**23.4 (11.6) (*n* = 8893)**	**4.602**	**0.032**	**0.000**
Verflt; M (SD)[b]	**29.3 (7.4) (*n* = 10)**	**21.0 (13.0) (*n* = 7754)**	**4.080**	**0.043**	**0.000**
Trla; M (SD)[a]	**52.6 (10.6) (*n* = 10)**	**72.9 (53.0) (*n* = 7204)**	**4.134**	**0.042**	**0.000**
MMSE; M (SD)[b]	**28.9 (2.3) (*n* = 7)**	**24.8 (4.5) (*n* = 6819)**	**5.511**	**0.019**	**0.000**

ADD-CNS, autoimmune demyelinating disease of the central nervous system; CAG, Cytosine-Adenine-Guanine repeat length; CAP-Score, CAG-Age Product-Index; HD, Huntington's disease; Hddiagn, Huntington's disease diagnosed; IS, Independence scale; MMSE, Mini-mental State Examination; SCNT, Stroop color naming test; SDMT, Symbol digit modality test; SIT, Stroop interference test; SWRT, Stroop word reading test; TFC, total functional capacity; TMS, total motor score; Trla, Trailmaking A test; UHDRS, Unified Huntington's Disease Rating Scale; Verfct, verbal fluency test (category); Verflt, verbal fluency test (Letters).
Bold values: significant differences between groups.
Cross-sectional data determining less motoric symptoms in manifest HD suffering from ADD-CNS and better cognitive performance in seven out of eight cognitive tests under immunomodulating therapies if compared with manifest other HD participants.
[a]Higher scores = more impairment.
[b]Higher scores = better performance.

neuroprotective effects in the patients identified here, resulting in better cognitive performances, although the number investigated was small and effects of GA alone could not be investigated.

The use of DMTs is effective to maintain cognitive test performance in relapsing-remitting MS.[47] One recent example is the use of the DMT siponimod, which can exhibit better cognitive performance in patients with secondary progressive MS in the Symbol digit modalities test (SDMT).[48] Thus, there is evidence from MS that the use of DMT can elicit positive effects on cognition.

Because HD is characterized with a loss of neurons due to degenerative processes, reactive microglial responses, and inflammation underlying the pathogenesis and progression, it is reasonable that, in addition, other identified immunomodulating therapies such as interferon

Table 5. ADD-CNS with no known immunomodulating therapies *versus* control at baseline visit.

	Manifest HD suffering from ADD-CNS group no immunomodulating therapies (*n* = 19)	**Manifest HD (*n* = 10,919)**	***F***	***p***	**Part. eta²**
Age (years); M (SD)	50.5 (11.1)	52.9 (12.8)	0.682	0.409	0.000
CAG high (SD)	42.9 (2.9)	44.0 (3.9) (*n* = 10,887)	1.393	0.238	0.000
CAP-Score (SD)	454.6 (112.7)	511.1 (99.3)	6.111	0.013	0.001
Motoric UHDRS TMS; M (SD)[a]	35.5 (26.2)	37.8 (21.5) (*n* = 10,781)	0.224	0.636	0.000
TFC; M (SD)[b]	8.2 (4.4)	8.2 (3.7) (*n* = 10,853)	0.001	0.977	0.000
IS; M (SD)[b]	74.2 (20.5)	77.0 (18.9) (*n* = 10,852)	0.381	0.537	0.000
SDMT; M (SD)[b]	29.0 (14.4)	23.0 (2.9) (*n* = 9937)	3.504	0.061	0.000
Verfct; M (SD)[b]	**15.7 (8.7)**	**12.0 (5.8) (*n* = 10,475)**	**7.650**	**0.006**	**0.000**
SCNT; M (SD)[b]	**50.2 (22.3)**	**41.7 (18.0) (*n* = 10,330)**	**4.062**	**0.044**	**0.000**
SWRT; M (SD)[b]	63.0 (27.5) (*n* = 18)	55.5 (23.6) (*n* = 10,281)	1.845	0.174	0.000
SIT; M (SD)[b]	28.5 (13.9)	23.4 (11.6) (*n* = 8893)	3.243	0.072	0.000
Verflt; M (SD)[b]	**28.7 (14.6) (*n* = 14)**	**21.0 (13.0) (*n* = 7754)**	**4.922**	**0.027**	**0.000**
Trla; M (SD)[a]	51.9 (33.7) (*n* = 11)	72.9 (53.0) (*n* = 7204)	1.725	0.189	0.000
MMSE; M (SD)[b]	24.9 (5.5) (*n* = 9)	24.8 (4.5) (*n* = 6819)	0.001	0.976	0.000

ADD-CNS, autoimmune demyelinating disease of the central nervous system; CAG, Cytosine-Adenine-Guanine repeat length; CAP-Score, CAG-Age Product-Index; HD, Huntington's disease; IS, Independence scale; MMSE, Mini-mental State Examination; SCNT, Stroop color naming test; SDMT, symbol digit modality test; SIT, Stroop interference test; SWRT, Stroop word reading test; TFC, total functional capacity; TMS, total motor score; Trla, Trailmaking A test; UHDRS, Unified Huntington's Disease Rating Scale; Verfct, verbal fluency test (category); Verflt, verbal fluency test (Letters). Cross-sectional data determined better cognitive performance in three out of eight cognitive tests in patients suffering from ADD-CNS with no known immunomodulating therapies if compared with manifest other HD participants.
Bold values: significant differences between groups.
[a]Higher scores = more impairment.
[b]Higher scores = better performance.

beta or fumaric acid might reveal beneficial effects on the course of HD.[49,50] Treatment with interferon beta had positive effects on cognitive impairment in a cohort of $n = 50$ patients[51] with relapsing multiple sclerosis and the oral dimethyl fumarate positively influences cognition in a cohort of $n = 217$ participants.[52] A partly longitudinal slowing of cognitive impairment was similarly accented in the cohort of HD-ADD-CNS patients investigated in this study revealing underlying positive

effects in to tests over time resulting in less progression compared with other motor-manifest HD patients.

Until now, no clinical intervention proved beneficial effects in HD or any other neurodegenerative disease.[53] Hence, there remains an urgent need to investigate promising candidate molecules in larger phase II clinical trials.

Another potential explanation to explain better cognitive performance in the cohort investigated here might be that specific factors in the cascade of chronic neuronal inflammation might have had not only negative, but also positive effects on neuronal cell death and neurodegenerative processes as neuroprotective factors in HD, clinically accompanied by better cognitive capacities in patients.[54] This hypothesis, also called 'protective autoimmunity' can be supported by data showing that an activation of the immune system and inflammation in neurodegenerative diseases is not solely mediating damage but activating regeneration and repair as protective factors in neurodegenerative diseases.[12] This effect might explain the positive effects on cognition also in the ADD-CNS group with no known immunomodulating therapy if compared with HD controls. As a second potential explanation, one might assume that at least some of the HD with ADD-CNS patients with no known medication received any immunomodulating therapy before having entered the ENROLL-HD study did not report about those therapies at inclusion or those therapies were not listed, because only therapies since inclusion were judged to be relevant by the investigator.

Limitations

As a limitation, the investigation of our clinical real-world data coming from an HD observational cohort does not allow further differentiation, because no other biological samples, imaging data, data regarding the course and severity of ADD-CNS disease like Expanded Disability Status Scale (EDSS) scores or diagnosis criteria (Mc Donald criteria 2017) are given within the ENROLL-HD study. Further underlying pathomechanisms within the cohorts and especially within the ADD-CNS cohorts might have had an undetected influence on the clinical course of the disease. Moreover, effects of specific DMTs especially in patients who received other DMTs and medications before analysis period of baseline assessment could not be analyzed due to low patient numbers. Especially the rather small number of patients in the real world and within the ENROLL-HD study suffering from demyelinating CNS diseases and additional HD are an important limitation prone to bias such as the possible recruiting limitation that patients with a more aggressive ADD-CNS might not be enrolled within ENROLL-HD due to potential difficulties to participate.

As a strength of the data presented here, data collection within the ENROLL-HD database offers a clear clinical registry design with standardized proceeding, leading to high-quality data used in this analysis. Further investigation regarding the clinical phenotype of coinciding ADD-CNS diseases which was conducted for the first time would not have been possible in another setting than a global multicenter approach. In addition to our analysis of data coming from manifest HD participants, we investigated two further cohorts of pre-manifest HD and HD-genotype negative participants suffering from ADD-CNS within the dataset, revealing more functional and motoric impairment during baseline and over time. Because these discrete differentiations were given within the dataset and presumptive comprehensible due to the additional ADD-CNS disease, we presume that our data of the manifest cohort illustrate realistic clinical findings and are not based on a systematic bias. To validate our findings, further clinical prospective studies with larger cohorts are necessary in a double-blinded clinical intervention.

As a conclusion, having analyzed the largest real-world cohort of HD patients, we show that patients suffering from motor-manifest HD and simultaneously from autoimmune demyelinating CNS diseases have better cognitive capacities in comparison to other motor-manifest HD patients. Moreover, the use of DMT might elicit positive effects in HD, although this effect might have been biased by a younger age in DMT-treated patients.

Declarations

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethic Committees of all study sites, which are part of the global multi-center longitudinal observational study ENROLL-HD. Each study site was required

to obtain and maintain local ethical approval. This study was registered at ClinicalTrials.gov with identifier: NCT01574053.

Consent for publication

Informed consent was obtained from all subjects involved in the study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Jannis Achenbach: Conceptualization; Data curation; Formal analysis; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Carsten Saft: Conceptualization; Data curation; Formal analysis; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Simon Faissner: Project administration; Supervision; Writing – original draft; Writing – review & editing.

Gisa Ellrichmann: Investigation; Project administration; Supervision; Writing – review & editing.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Appendix 1. Propensity score matching for all manifest HD subjects suffering from ADD-CNS.

Domain/variable	Manifest HD suffering from ADD-CNS *n* = 32	Manifest HD *n* = 96	*t*	*p*	Coefficients (Cohen's *d*/Chi-Quadrat)
Age (years); M (SD)	49.3 (10.3)	49.2 (11.6)	0.041	0.968	11.30
CAG; M (SD)	43.5 (2.9)	43.6 (2.8)	0.215	0.830	2.847
Sex (f/m) (%f)	21/11 (65.6)	65/31 (67.7)	NA	0.831	0.047
ISCED	3.4 (1.3)	3.3 (1.2)	0.342	0.733	1.195
Region (Australasia/Europe/ Latin America/Northern America) (%Europe)	0/26/0/6 (81.3)	1/64/1/30 (66.7)	NA	0.346	2.726
UHDRS TMS; M (SD)[a]	32.1 (24.3)	34.3 (18.3)	−0.534	0.594	19.981
TFC; M (SD)[b]	8.6 (3.9)	8.4 (3.0)	0.233	0.816	3.280
IS; M (SD)[b]	76.1 (20.2)	79.1 (14.0)	−0.770	0.445	15.799
SDMT[b]	**28.8 (13.3) (*n* = 29)**	**21.2 (10.6) (*n* = 93)**	**3.601**	**<0.001**	**11.000**
Verfct[b]	14.3 (8.0)	12.2 (5.0) (*n* = 95)	1.401	0.169	5.906
SCNT[b]	**48.9 (20.4) (*n* = 31)**	**38.6 (13.1) (*n* = 95)**	**3.910**	**<0.001**	**14.586**
SWRT[b]	**62.5 (25.3) (*n* = 31)**	**51.0 (18.7) (*n* = 94)**	**2.727**	**<0.050**	**20.525**
SIT[b]	**28.2 (13.5) (*n* = 30)**	**21.8 (9.1) (*n* = 85)**	**2.903**	**<0.005**	**10.420**
VerFc[b]	**27.1 (13.2) (*n* = 24)**	**20.8 (11.5) (*n* = 78)**	**2.293**	**<0.050**	**5.906**
MMSE[b]	26.3 (4.7) (*n* = 15)	24.4 (3.9) (*n* = 74)	1.691	0.094	4.111
Trla[a]	56.0 (49.1) (*n* = 21)	80.7 (56.6) (*n* = 75)	−1.790	0.077	55.951

ADD-CNS, autoimmune demyelinating disease of the central nervous system; CAG, Cytosine-Adenine-Guanine repeat length; HD, Huntington's disease; IS, Independence scale; ISCED, Educational level; MMSE, Mini-mental State Examination; SCNT, Stroop color naming test; SD, standard deviation; SDMT, symbol digit modality test; SIT, Stroop interference test; SWRT, Stroop word reading test; TFC, total functional capacity; TMS, total motor score; Trla, Trailmaking A test; UHDRS, Unified Huntington's Disease Rating Scale; VerFc, verbal fluency test (Letters); Verfct, verbal fluency test (category). Bold values: significant differences between groups.
ADD-CNS HD patients were matched 1:3 to manifest HD patients. Age, CAG, sex, and ISCED were used for calculating propensity scores.
[a]Higher scores = more impairment.
[b]Higher scores = better performance.

Appendix 2. Propensity score matching for pre-manifest HD subjects suffering from ADD-CNS.

Domain/variable	Pre-manifest HD suffering from ADD-CNS *n* = 12	Pre-manifest HD *n* = 36	*t*	*p*	Coefficients (Cohen's *d*/Chi-Quadrat)
Age (years); M (SD)	43.7 (9.8)	43.0 (12.2)	0.027	0.870	11.69
CAG; M (SD)	41.0 (1.3)	41.0 (1.4)	0.000	1.00	1.38
Sex (f/m) (%f)	11/1 (91.7)	32/ 4 (88.9)	NA	0.633	0.785
ISCED	4.1 (1.2)	4.2 (1.2)	0.281	0.780	1.18
Region (Australasia/Europe/ Northern America) (%Europe)	0/6/6 (50)	3/23/10 (63.9)	NA	0.270	2.621
UHDRS TMS; M (SD)[a]	3.7 (5.3)	1.9 (2.5)	1.12	0.281	3.38
TFC; M (SD)[b]	12.5 (0.9)	12.9 (0.3)	−1.66	0.122	0.529
IS; M (SD)[b]	96.7 (6.1)	100.0 (0.0)	−1.88	0.087	3.010
SDMT[b]	49.0 (15.0)	50.0 (10.0)	0.256	0.799	11.382
Verfct[b]	23.0 (6.7)	21.8 (6.1)	0.556	0.581	6.295
SCNT[b]	65.6 (19.2)	75.7 (14.5)	−1.92	0.061	15.781
SWRT[b]	85.6 (27.0)	94.1 (13.9)	−1.04	0.351	17.962
SIT[b]	41.2 (11.8)	44.4 (10.2) (*n* = 34)	−0.915	0.365	10.662
VerFc[b]	39.2 (14.1) (*n* = 11)	39.6 (14.1) (*n* = 31)	−0.094	0.927	14.086
MMSE[b]	28.1 (2.3) (*n* = 7)	28.9 (1.3) (*n* = 27)	−0.879	0.409	1.507
Trla[a]	30.0 (11.1) (*n* = 11)	26.4 (10.0) (*n* = 30)	0.993	0.327	10.287

ADD-CNS, autoimmune demyelinating disease of the central nervous system; CAG, Cytosine-Adenine-Guanine repeat length; HD, Huntington's disease; IS, Independence scale; ISCED, Educational level; MMSE, Mini-mental State Examination; SCNT, Stroop color naming test; SDMT, symbol digit modality test; SIT, Stroop interference test; SWRT, Stroop word reading test; TFC, total functional capacity; TMS, total motor score; Trla, Trailmaking A test; UHDRS, Unified Huntington's Disease Rating Scale; VerFc, verbal fluency test (Letters); Verfct, verbal fluency test (category). ADD-CNS HD patients were matched 1:3 to manifest HD patients. Age, CAG, sex, and ISCED were used for calculating propensity scores.
[a]Higher scores = more impairment.
[b]Higher scores = better performance.

Appendix 3. Propensity score matching for manifest HD subjects suffering from ADD-CNS with immunomodulating therapies.

Domain/variable	Manifest HD suffering from ADD-CNS group with immunomodulating therapies *n* = 12	Manifest HD *n* = 36	*t*	*p*	Coefficients (Cohen's *d*/Chi-Quadrat)
Age (years); M (SD)	45.2 (8.5)	42.4 (8.7)	1.00	0.322	0.33
CAG; M (SD)	44.4 (2.9)	46.0 (3.6)	−1.39	0.170	−0.46
Sex (f/m) (%f)	7/5 (58.3)	25/11 (69.4)	NA	0.356	0.500
ISCED	3.3 (0.9)	3.4 (0.9)	−0.08	0.933	−0.03
Region (Europe/Northern America) (%Europe)	11/1 (91.7)	43/5 (89.6)	NA	0.633	0.074
UHDRS TMS; M (SD)[a]	21.7 (15.5)	34.1 (19.9)	−1.95	0.057	−0.65
TFC; M (SD)[b]	9.8 (2.4)	9.3 (3.3)	0.48	0.630	0.162
IS; M (SD)[b]	83.7 (13.3)	82.4 (16.8)	0.26	0.797	0.086
SDMT[b]	**31.4 (10.2)**	**22.1 (11.5) (*n* = 34)**	**2.48**	**0.017**	**0.834**
Verfct[b]	14.5 (7.3)	12.3 (4.2)	1.24	0.220	0.416
SCNT[b]	**52.6 (12.7)**	**39.6 (14.8)**	**2.71**	**0.009**	**0.908**
SWRT[b]	**69.9 (19.0)**	**51.8 (21.5)**	**2.59**	**0.013**	**0.865**
SIT[b]	30.8 (11.4)	24.2 (10.6) (*n* = 29)	1.78	0.082	0.613
VerFc[b]	**29.4 (7.8) (*n* = 9)**	**20.2 (11.5) (*n* = 26)**	**2.21**	**0.034**	**0.856**
MMSE[b]	28.7 (2.4) (*n* = 6)	25.7 (3.6) (*n* = 21)	1.92	0.067	0.887
Trla[a]	**36.9 (9.2) (*n* = 9)**	**68.6 (31.9) (*n* = 24)**	**−4.40**	**<0.001**	**−1.136**

ADD-CNS, autoimmune demyelinating disease of the central nervous system; CAG, Cytosine-Adenine-Guanine repeat length; HD, Huntington's disease; IS, Independence scale; ISCED, Educational level; MMSE, Mini-mental State Examination; SCNT, Stroop color naming test; SDMT, symbol digit modality test; SIT, Stroop interference test; SWRT, Stroop word reading test; TFC, total functional capacity; TMS, total motor score; Trla, Trailmaking A test; UHDRS, Unified Huntington's Disease Rating Scale; VerFc, verbal fluency test (Letters); Verfct, verbal fluency test (category). ADD-CNS HD patients were matched 1:3 to manifest HD patients. Age, CAG, sex, and ISCED were used for calculating propensity scores. Bold values: significant differences between groups.
[a]Higher scores = more impairment.
[b]Higher scores = better performance.