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Cognitive engagement may slow clinical progression and brain atrophy in Huntington's disease

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Key points

An early cognitively active lifestyle can confer benefits to preserved motor and psychiatric function in addition to cognitive performance in Huntington's disease. 2) More cognitively active individuals show decreased gray matter volume atrophy (e.g., brain maintenance) in the medial frontal gyrus, supplementary area, and middle cingulate cortex at longitudinal follow-up. 3) Such brain regions may act as neural hubs in circuits that integrate functionally diverse processes spanning cognitive, motor, and psychiatric domains.

Lifelong cognitive engagement conveys benefits in Huntington's disease (HD) and may positively affect non-cognitive domains in other populations. However, the effect of lifelong cognitive engagement on the progression of motor and psychiatric domains in HD remains unknown, as is its neurobiological basis. Forty-five HD individuals completed the Cognitive Reserve Questionnaire (CRQ) and longitudinal clinical evaluation (maximum total of six visits, mean inter-assessment duration of 13.53 ± 4.1 months). Of these, thirty-three underwent longitudinal neuroimaging (18 ± 6 months follow-up). Generalized linear mixed-effects models were executed to predict the effect of individual differences in lifelong cognitive engagement on HD clinical progression and voxel-based morphometry to explore the impact of lifelong cognitive engagement on whole-brain gray matter volume atrophy. Controlling for age, disease stage, and sex, higher CRQ scores were associated with reduced overall severity and longitudinal progression across cognitive, motor, and psychiatric domains. Those with higher CRQ scores demonstrated reduced gray matter volume loss in the middle frontal gyrus, supplementary motor area, and middle cingulate. This putative impact on HD clinical progression may be conferred by preservation of brain volume in neural hubs that integrate executive function with action initiation and behavioral regulation, providing support for early cognitive engagement, even prior to diagnosis.

Keywords Brain maintenance, Cognitive engagement, Gray matter volume, Huntington's disease, Longitudinal, Neurodegeneration

Abbreviations

BA	Brodmann area
CAP	standardized CAG-Age Product
CRQ	Cognitive Reserve Questionnaire
GMV	gray matter volume
HD	Huntington's disease
MFG	superior medial frontal gyrus
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging

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PBA-s	short-Problem Behavior Assessment
SMA	supplementary motor area
UHDRS-cogscore	Unified Huntington's Disease Rating Scale total cognitive score
UHDRS-motor	Unified Huntington's Disease Rating Scale total motor score
VBM	voxel-based morphometry

The progression of cognitive decline demonstrates great inter-individual variability throughout the period of aging and dementia[1]. Although precipitating factors remain controversial, such heterogeneity may be explained by variability in cognitive lifestyle, including education, occupation or engagement in cognitive activities[2–5]. Studies suggest that an active cognitive lifestyle can reduce deficits in aging[6]and neurodegenerative diseases[7–9], including Huntington's disease (HD)[10,11]. Nonetheless, the neurological underpinnings of this phenomenon remain to be elucidated, particularly longitudinally.

HD is a neurodegenerative disorder caused by a CAG repeat expansion in the *HTT*gene[12,13], in that those with a greater number of CAG repeats are associated with an earlier onset and more severe manifestation of the disease. The disorder typically manifests in mid-adulthood, with degeneration beginning in the striatum and extending to other subcortical and cortical regions[14]. This later gives rise to a triad of motor, cognitive, and psychiatric symptoms that increasingly impact functional capacity as the disease progresses. Because predictive genetic testing can identify individuals that will later develop HD, the disease is unique in that it may serve as a model to study the general neurodegenerative process before clinical onset.

In this vein, CAG repeat length is inversely related to the age of motor onset and directly to the rate of clinical progression of motor, cognitive, and functional symptoms[15,16]. However, there is inter-individual heterogeneity in specific clinical manifestations, giving rise to variable symptom profiles that may be due in part to variability in neurodegenerative patterns[17]. With CAG repeats only accounting for ~ 56% of variability in age of onset[18], modulatory genes and life experiences may additionally impact inter-individual differences in age of onset, initial symptom presentation, and HD progression[19,20]. Nonetheless, the precise lifestyle factors that impart this variability remain under study.

Traditionally, lifelong cognitive engagement (e.g., educational and occupational attainment, cognitively stimulating leisure, and social activities) has been related with increased cognitive performance and executive function, in both old age[21]and neurodegenerative disease[7]. In Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, those with higher education levels remain asymptomatic for longer and display slower rates of cognitive decline[22–26].

Recently, the benefits of cognitive reserve have been shown to extend to other functional domains, including motor and behavioral. For example, studies in neurodegenerative populations suggest that an active cognitive lifestyle can reduce clinical decline in motor deficits in Parkinson's disease[27,28]and amyotrophic lateral sclerosis[29]. This may be due to the fact that motor output relies on neural circuits that integrate action execution with motor planning and control. Meanwhile, the risk of developing psychiatric disorders such as schizophrenia are higher in those with low cognitive reserve[30,31]. Certain psychiatric disturbances, such as apathy, have long been linked to cognitive dysfunction[32–35]. In this vein, the reverse may be true, in that higher cognitive reserve may protect against mental health affliction[36], including depression[37]and apathy[38]. Given this cumulative evidence, it is plausible that cognitively stimulating activities may positively influence non-cognitive domains, warranting further study.

Converging evidence for cognitive reserve is seen in HD; however, the majority of research is limited to effects in the cognitive domain. In particular, greater lifelong cognitive engagement has been associated with slower rates of cognitive symptom progression over time in both premanifest[39]and early manifest HD individuals[11]. Another study found that an early cognitively active lifestyle predicted both delayed clinical symptom onset and less severe cognitive deficits in HD gene-carriers[10]. Conversely, a passive cognitive lifestyle is related to early HD onset[40].

Recently, other symptom domains have been investigated in HD individuals. Specifically, a cross-sectional study found that manifest patients with more education demonstrate an earlier self-reported age of onset of motor, cognitive, depressive, and irritable symptoms, in contrast to more preserved objective functional assessment and motor exam scores[41]. These findings corroborate past literature in HD, additionally revealing a link between more years of schooling and less behavioral impairment[42]. The authors attributed these findings to an earlier recognition of symptom onset by more educated individuals, while better performance was potentially explained by the protective effect of cognitive reserve in those with more education. In addition, bilingualism, a component of cognitive reserve, was associated with improved performance in inhibitory control and set-shifting in HD[43].

Overall, however, there is a paucity of knowledge regarding the neural mechanisms underlying the effects of cognitive engagement in HD. On the one hand, existing whole-brain analyses are solely cross-sectional[10,43]and, while providing useful information, therefore cannot address causal links. Meanwhile, one longitudinal study that analyzes the neural correlates of cognitive engagement in HD focuses only on the striatum[39], despite the fact that HD affects other brain regions[14], and is limited in its assessment of strictly cognitive symptomology.

Elucidating the neural underpinnings of cognitive engagement may bear evidence for neural resilience beyond passive brain reserve. In this way, resilience has been defined as encompassing brain reserve, brain maintenance, and compensation[5]. Lifelong cognitive enrichment may confer a beneficial impact on brain maintenance (e.g., resistance to brain atrophy) or functional compensation (e.g., plasticity, adaptability, flexibility)[44–47]. Recently, a longitudinal framework for compensation was operationalized and later tested in HD with both structural and functional neuroimaging measures[48,49]. Furthermore, beneficial lifestyle factors were associated with lower serum levels of neurofilament light protein, a biochemical marker of neuronal damage that can be used as a measure of HD progression[50]. Such evidence substantiates the neuroplastic nature of the

brain, in which environmental factors (e.g., cognitive enrichment, neural insult) can positively or negatively impact brain resistance or resilience. Of neuroimaging measures, structural MRI (i.e., brain volume) has been highlighted as one of the most sensitive proxies of brain reserve capacity[46]. At this time, there is a need for longitudinal whole-brain studies, which can examine the relationship between cognitive engagement and brain maintenance, or even enhancement, over time.

As such, the current study implements a longitudinal approach to investigate the effect of an early active cognitive lifestyle on HD progression across the spectrum of clinical manifestations (cognitive, motor, and psychiatric) and the neural changes sustaining these effects. More specifically, we first employed generalized linear mixed-effects models to study the rate of symptom progression in relation to a composite cognitive reserve score including education, occupation, and engagement in cognitive activities. Second, we shed light on how such lifelong cognitive engagement may impact brain maintenance over time at the whole-brain level using longitudinal voxel-based morphometry (VBM). Overall, we hypothesized that HD gene-carriers who practiced a more cognitively active lifestyle from an early age will manifest slower deterioration of cognitive, motor, and possibly psychiatric dysfunction. We also expected that higher cognitive reserve scores would be associated with regional brain maintenance, that is, a lower loss of GMV. Such brain maintenance may be evidenced as a reduction in atrophy in regions initially targeted by disease pathology (e.g., striatum) as well as a preservation of volume in brain areas that have been recruited to sustain clinical function.

Results

The VBM cohort is characterized in Supplementary Table 1. Longitudinal raw data are depicted in Supplementary Fig. 1.

Generalized linear mixed-effects models

For all three sets of models, the likelihood ratio test between the null and the alternative model indicated that the latter (containing the CRQ score and interaction term as predictor variables) was a better fit in predicting longitudinal UHDRS-cogscore ($\chi^2[2]=12.2$, $P=0.002$), UHDRS-motor ($\chi^2[2]=13.2$, $P=0.001$), and PBA-s scores ($\chi^2[2]=16.0$, $P<0.001$) at the individual level (Fig. 1). This finding is further evidenced through the superior Akaike's information criteria weight for the alternative models when compared to the null (Table 1).

When evaluating individual variables (Table 1), the CRQ score demonstrated a significant influence in all three alternative models. Specifically, a higher CRQ score independently predicted preserved overall functioning across domains over time (i.e., higher UHDRS-cogscores and lower UHDRS-motor and PBA-s scores). Of note, the interaction term between CRQ and time was also significant in all three models, indicating a relationship between CRQ score and the progression of cognitive, motor, and psychiatric dysfunction over time (Fig. 1).

In addition, the relationship between CRQ scores and individual subdomains of the UHDRS-cogscore was assessed (Table 2; Fig. 2). Similarly, the likelihood ratio test between the null and the alternative model indicated that the latter (containing the CRQ score and interaction term as predictor variables) was a better fit in predicting longitudinal scores on the F-A-S test ($\chi^2[2]=9.8$, $P=0.007$), Symbol Digit Modalities Test ($\chi^2[2]=14.5$, $P<0.001$), and Stroop interference ($\chi^2[2]=11.8$, $P=0.003$) at the individual level. Again, the interaction term between CRQ and time was also significant in all three models, indicating a relationship between CRQ score and the progression of each of the cognitive domains.

Later, when evaluating the relationship between CRQ scores and individual subdomains of the PBA-s (Table 3; Fig. 3), the likelihood ratio test between the null and the alternative model indicated that the latter

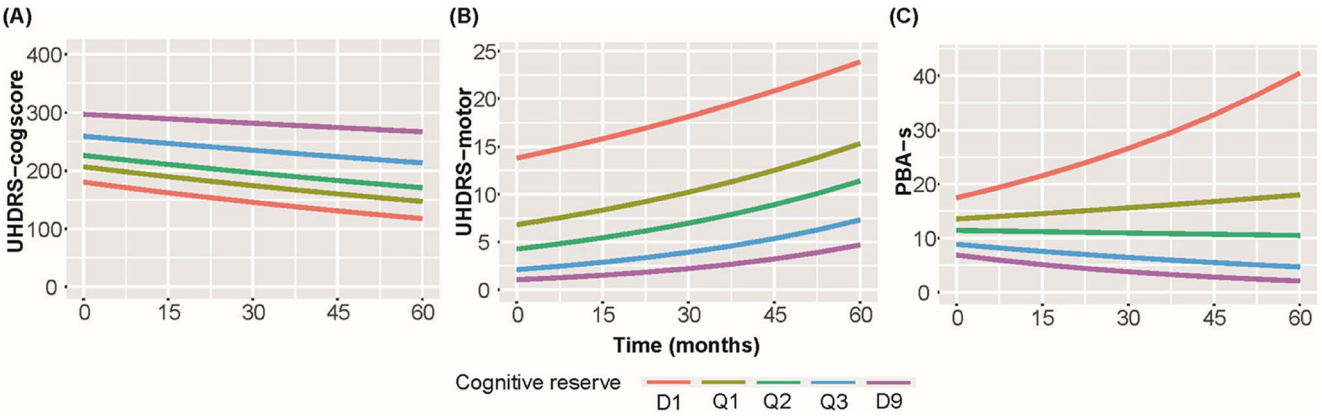

Fig. 1. Higher Cognitive Reserve Questionnaire scores predict lower overall severity and rate of progression across time and symptom domains. Plots depict the prediction of the different models over time grouped by the different levels (quartiles and deciles) of lifelong cognitive engagement. Plot (**A**) represents cognitive decline (Model 1.1), plot (**B**) motor symptoms (Model 2.1), and plot (**C**) psychiatric disturbances (Model 3.1). Image generated with sjPlot package in R v.4.4.0. D1 = first decile; Q1 = first quartile; Q2 = median; Q3 = third quartile; D9 = ninth decile; PBA-s = short-Problem-Behavior Assessment; UHDRS-cogscore = Unified Huntington's Disease Rating Scale total cognitive score; UHDRS-motor = Unified Huntington's Disease Rating Scale total motor score.

	β Estimate	*SE*	95% CI	*Z* value	*P* value
Model 1.0 – UHDRS-cogscore null AIC = 1540.6; *W* = 0.017					
CAP	-0.197	0.065	[-0.32, -0.07]	-3.03	0.003**
Time[a]	-0.051	0.030	[-0.11, 0.01]	-1.71	0.087
Sex	-0.003	0.060	[-0.12, 0.11]	-0.05	0.958
Model 1.1 – UHDRS-cogscore CRQ AIC = 1532.5; *W* = 0.983					
CAP	-0.154	0.061	[-0.27, -0.04]	-2.53	0.011*
Time[a]	-0.060	0.027	[-0.11, -0.01]	-2.23	0.026*
Sex	-0.039	0.055	[-0.15, 0.07]	-0.71	0.476
CRQ	0.233	0.065	[0.11, 0.36]	3.58	<0.001***
CRQ × Time[a]	0.056	0.024	[0.01, 0.10]	2.34	0.019*
Model 2.0 – UHDRS-motor null AIC = 1154.2; *W* = 0.010					
CAP	1.108	0.219	[0.68, 1.54]	5.06	<0.001***
Time[a]	0.163	0.075	[0.02, 0.31]	2.16	0.031*
Sex	0.057	0.234	[-0.40, 0.52]	0.24	0.809
Model 2.1 – UHDRS-motor CRQ AIC = 1145.0; *W* = 0.990					
CAP	0.978	0.201	[0.58, 1.37]	4.86	<0.001***
Time[a]	0.207	0.073	[0.07, 0.35]	2.86	0.004**
Sex	0.155	0.207	[-0.25, 0.56]	0.75	0.453
CRQ	-0.749	0.218	[-1.18, -0.32]	-3.43	<0.001***
CRQ × Time[a]	0.096	0.045	[0.01, 0.18]	2.15	0.031*
Model 3.0 – PBA-s null AIC = 1771.8; *W* = 0.003					
CAP	0.107	0.166	[-0.22, 0.43]	0.65	0.519
Time[a]	-0.066	0.120	[-0.30, 0.17]	-0.55	0.582
Sex	-0.304	0.173	[-0.64, 0.04]	-1.75	0.080[†]
Model 3.1 – PBA-s CRQ AIC = 1759.8; *W* = 0.997					
CAP	-0.039	0.154	[-0.34, 0.26]	-0.26	0.798
Time[a]	-0.048	0.115	[-0.27, 0.18]	-0.42	0.673
Sex	-0.200	0.157	[-0.51, 0.11]	-1.28	0.202
CRQ	-0.618	0.162	[-0.94, -0.30]	-3.81	<0.001***
CRQ × Time[a]	-0.234	0.117	[-0.46, -0.01]	-2.00	0.046*

Table 1. Cognitive, motor, and psychiatric function as independently predicted by CRQ score in combined HD group. All regression estimates are standardized. **P*-values significant at $P<0.05$. ***P*-values significant at $P<0.01$. ****P*-values significant at $P<0.001$. [†]*P*-values approaching significance. [a]Time in days (accumulative, time at first assessment is zero). AIC=Akaike's information criteria; CAP=standardized CAG-age product[87]; CRQ=Cognitive Reserve Questionnaire[91]; HD=Huntington's disease; PBA-s=short-Problem Behavior Assessment; UHDRS-cogscore=Unified Huntington's Disease Rating Scale total cognitive score[102]; UHDRS-motor=Unified Huntington's Disease Rating Scale total motor score; *W*=Akaike's information criteria weight[97,98].

(containing the CRQ score and interaction term as predictor variables) was a better fit in predicting longitudinal scores in all domains assessed. Namely, this entailed a statistically significant relationship between CRQ and overall severity of apathy ($\chi^2[2]=11.5$, $P=0.003$) and dysexecutive behaviors ($\chi^2[2]=12.8$, $P=0.002$) over time. Meanwhile, while not reaching statistical significance, a trend to the effect was exhibited for mood disturbances ($\chi^2[2]=5.2$, $P=0.076$) and irritability/aggression ($\chi^2[2]=5.5$, $P=0.066$).

Lastly, we extended the analyses to examine the relationship between CRQ and clinical progression for manifest and premanifest groups separately. In manifest HD participants, the alternative model was superior for UHDRS-motor ($\chi^2[2]=7.0$, $P=0.030$). For the psychiatric disturbances, the alternative model was superior for overall PBA-s scores ($\chi^2[2]=9.4$, $P=0.009$) and mood ($\chi^2[2]=9.2$, $P=0.010$) in particular. Of the cognitive domains, the alternative model was superior specifically for the Stroop interference test ($\chi^2[2]=7.0$, $P=0.031$). Meanwhile, in premanifest HD gene-expansion carriers, the alternative model was superior for UHDRS-cogscore ($\chi^2[2]=9.1$, $P=0.010$), including the F-A-S test specifically ($\chi^2[2]=10.6$, $P=0.005$). When examining psychiatric disturbances, the alternative model was superior for overall PBA-s scores ($\chi^2[2]=9.3$, $P=0.010$) as well as apathy ($\chi^2[2]=7.1$, $P=0.029$) and dysexecutive behaviors ($\chi^2[2]=8.3$, $P=0.019$).

	β Estimate	*SE*	95% CI	*Z* value	*P* value
Model 1a.0 – F-A-S test null AIC = 1347.3; *W* = 0.052					
CAP	-0.165	0.066	[-0.29, -0.04]	-2.52	0.012*
Time[a]	-0.029	0.031	[-0.09, 0.03]	-0.95	0.341
Sex	-0.044	0.062	[-0.16, 0.08]	-0.71	0.480
Model 1a.1 – F-A-S test CRQ AIC = 1341.5; *W* = 0.948					
CAP	-0.128	0.063	[-0.25, -0.01]	-2.04	0.042*
Time[a]	-0.039	0.028	[-0.09, 0.02]	-1.37	0.170
Sex	-0.072	0.059	[-0.19, 0.04]	-1.22	0.224
CRQ	0.213	0.068	[0.08, 0.35]	3.12	0.002**
CRQ × Time[a]	0.054	0.025	[0.01, 0.10]	2.19	0.029*
Model 1b.0 – Stroop interference null AIC = 1311.7; *W* = 0.020					
CAP	-0.248	0.073	[-0.39, -0.11]	-3.41	<0.001***
Time[a]	-0.053	0.034	[-0.12, 0.01]	-1.56	0.120
Sex	0.036	0.072	[-0.11, 0.18]	0.50	0.618
Model 1b.1 – Stroop interference CRQ AIC = 1303.9; *W* = 0.980					
CAP	-0.203	0.071	[-0.34, -0.06]	-2.86	0.004**
Time[a]	-0.065	0.031	[-0.13, -0.01]	-2.12	0.034*
Sex	0.008	0.069	[-0.13, 0.14]	0.11	0.910
CRQ	0.219	0.072	[0.08, 0.36]	3.05	0.002**
CRQ × Time[a]	0.071	0.026	[0.02, 0.12]	2.71	0.007**
Model 1c.0 – SDMT null AIC = 1320.6; *W* = 0.005					
CAP	-0.122	0.058	[-0.24, -0.01]	-2.09	0.036*
Time[a]	-0.092	0.033	[-0.16, -0.03]	-2.79	0.005**
Sex	-0.025	0.051	[-0.12, 0.08]	-0.49	0.627
Model 1c.1 – SDMT CRQ AIC = 1310.1; *W* = 0.995					
CAP	-0.107	0.053	[-0.21, -0.003]	-2.02	0.043*
Time[a]	-0.094	0.029	[-0.15, -0.04]	-3.19	0.001**
Sex	-0.048	0.049	[-0.14, 0.05]	-1.00	0.318
CRQ	0.287	0.073	[0.14, 0.43]	3.95	<0.001***
CRQ × Time[a]	0.804	0.026	[0.03, 0.13]	3.08	0.002**

Table 2. Individual cognitive items as independently predicted by CRQ score in combined HD group. All regression estimates are standardized. **P*-values significant at $P<0.05$. ***P*-values significant at $P<0.01$. ****P*-values significant at $P<0.001$. †*P*-values approaching significance. [a]Time in days (accumulative, time at first assessment is zero). AIC=Akaike's information criteria; CAP=standardized CAG-age product[87]; CRQ=Cognitive Reserve Questionnaire[91]; HD=Huntington's disease; SDMT=Symbol Digit Modalities Test; *W*=Akaike's information criteria weight[97,98].

VBM results

CRQ scores were found to negatively correlate with measures of GMV atrophy, controlling for covariates of no interest including CAP (a proxy for disease stage including age and CAG repeats), time between scans (days), and total intracranial volume and correcting for multiple comparisons at cluster-level. In particular, higher levels of lifelong cognitive engagement were significantly associated with a lower loss of GMV over time. This effect was specific to the right superior medial frontal gyrus (MFG; *cluster size* = 906, T = 6.04, $P<0.001$, MNI [x = 11, y = 27, z = 48]) extending to the supplementary motor area (SMA; MNI [x = 14, y = 8, z = 56]) and middle cingulate cortex (MCC; MNI [x = 17, y = 3, z = 47]) (Fig. 4). In post hoc analysis additionally controlling for sex, linear regression showed the region of interest to maintain the effect (small volume correction; *cluster size* = 228, T = 5.22, $P<0.001$), MNI [x = 11, y = 27, x = 48]). For cross-sectional VBM results, see previous work[10].

Discussion

The present longitudinal study aimed to delineate the impact of an early cognitively active lifestyle in HD gene-carriers on, first, the progression of cognitive, motor, and psychiatric functioning and, second, potential underlying structural brain maintenance. Utilizing generalized linear mixed-effects models, we found that variability in levels of lifelong cognitive engagement may explain individual differences in clinical progression in motor and psychiatric domains in addition to cognitive performance. Furthermore, we elucidated that such

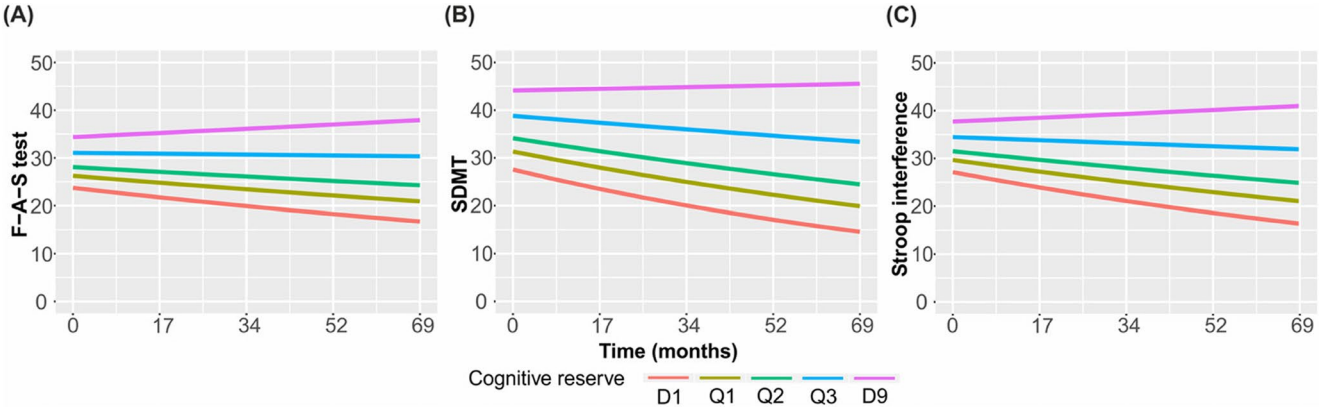

Fig. 2. Higher Cognitive Reserve Questionnaire scores predict lower overall severity and rate of progression across time for cognitive domains, namely the F-A-S test (**A**), SDMT (**B**), and Stroop interference (**C**). Plots depict the prediction of the different models over time grouped by the different levels (quartiles and deciles) of lifelong cognitive engagement. Image generated with sjPlot package in R v.4.4.0. D1 = first decile; Q1 = first quartile; Q2 = median; Q3 = third quartile; D9 = ninth decile; SDMT = Symbol Digit Modalities Test.

lifestyle factors may be related to brain maintenance in functionally connected hubs. Specifically, individuals with higher cognitive reserve demonstrated a lower rate of GMV loss in the MFG, SMA, and MCC, executive regions that contribute to the integration of cognitive, motor, and psychiatric function.

First, lifelong cognitive engagement was found to be associated with a greater overall preservation of cognitive, motor, and psychiatric functioning, even after controlling for CAP (proxy for disease stage), as delineated by the generalized-linear mixed effects models. This indicates that, even at the same disease stage, the overall CRQ score and interaction term between CRQ score and time predicted the longitudinal severity and progression of UHDRS-cogscore, UHDRS-motor, and PBA-s scores.

When extending analyses to consider manifest and premanifest individuals separately, it was found that, in manifest individuals, greater lifelong cognitive engagement most predicted preserved motor and psychiatric (especially mood) functioning and specifically inhibitory control (i.e., Stroop interference) in the cognitive domain. Meanwhile, premanifest individuals with higher CRQ scores demonstrated more preserved functioning in phonetic verbal fluency and overall cognitive functioning, as well as more preserved behavioral functioning (especially apathy and dysexecutive behaviors).

Regarding cognitive symptoms, individuals with higher levels of lifelong cognitive engagement demonstrated more preserved cognitive faculties across time. These findings are in line with past literature in HD, in that a more cognitively active lifestyle (as measured by education, occupation, and premorbid intelligence) was related to a slower decline in cognitive set switching[39]. Converging evidence, albeit cross-sectional, further exemplifies significant associations between an active cognitive lifestyle and working memory, inhibitory control, and cognitive flexibility in HD[10]. Meanwhile, a recent study demonstrated that higher cognitive functioning was predicted by greater cognitive reserve specifically in leisure activities, but not necessarily work and education[11].

Furthermore, the present findings demonstrate that a more cognitively active lifestyle at an early age was also related to more preserved motor performance over time, particularly in the combined and manifest cohorts. Similar findings have been reported in HD at the cross-sectional level in terms of preserved motor function[41,42]and delayed motor symptom onset[10]. Such work is further evidenced in transgenic mouse models of HD, whereby environmental enrichment has been shown to significantly delay motor symptom onset[51,52], while positively influencing motor performance[19,53,54]. Overall, these results elucidate the transference of early cognitive engagement to the preservation of motor abilities in HD, as has been previously illustrated in Parkinson's disease[28,55], with the present findings extending such findings to longitudinal motor symptom progression.

Lastly, and in a similar manner, greater lifelong cognitive engagement predicted those individuals who would demonstrate improved psychiatric outcomes over time. The link between dementia and psychiatric dysfunction has long been demonstrated. Specifically, depression and apathy are associated with a greater risk of cognitive decline[56–58]. As such, it follows that heightened cognitive reserve may be protective against behavioral disturbances[30,38,59,60]. In HD, more years of schooling has been linked with less severe psychiatric disturbances using the UHDRS-behavior subscale[42], but not with self-reported onset and severity of psychiatric disturbances[41]. In this way, the state of the current literature supports continued study of the relationship between cognitive engagement and psychiatric dysfunction using validated, externally administered scales, especially in individuals prone to anosognosia, such as in HD, where features such as apathy may be underreported[41,61].

When examining structural brain changes, longitudinal VBM analysis revealed that a more active cognitive lifestyle at an early age was related with higher levels of brain resistance. Specifically, we found a slower rate of GMV atrophy in the right MFG extending to the SMA and MCC, regions involved in cognitive functions. In particular, the MFG and MCC (BA32, also known as the dorsal anterior cingulate) take part in the executive control circuit, modulating processes such as task-switching, prevention of interference, and inhibitory control[62,63]. Additionally, the SMA has been shown to be involved in classical cognitive operations such as spatial processing, numerical cognition, working memory, and language production and comprehension[64,65].

	β Estimate	*SE*	95% CI	*Z* value	*P* value
Model 3a.0 – Mood null AIC = 1159.6; *W* = 0.360					
CAP	-0.381	0.213	[-0.80, 0.04]	-1.79	0.074†
Time[a]	-0.177	0.182	[-0.53, 0.18]	-0.97	0.331
Sex	-0.065	0.217	[-0.49, 0.36]	-0.30	0.766
Model 3a.1 – Mood CRQ AIC = 1158.5; *W* = 0.640					
CAP	-0.436	0.221	[-0.87, -0.004]	-1.98	0.048*
Time[a]	-0.164	0.173	[-0.50, 0.18]	-0.95	0.343
Sex	-0.034	0.217	[-0.46, 0.39]	-0.16	0.875
CRQ	-0.394	0.234	[-0.85, 0.07]	-1.68	0.093†
CRQ × Time[a]	-0.351	0.167	[-0.68, -0.02]	-2.10	0.036*
Model 3b.0 – Apathy null AIC = 955.5; *W* = 0.023					
CAP	0.306	0.217	[-0.12, 0.73]	1.41	0.159
Time[a]	-0.113	0.159	[-0.42, 0.20]	-0.71	0.478
Sex	-0.598	0.291	[-1.17, -0.03]	-2.06	0.040*
Model 3b.1 – Apathy CRQ AIC = 948.1; *W* = 0.977					
CAP	0.159	0.210	[-0.25, 0.57]	0.76	0.447
Time[a]	-0.134	0.160	[-0.45, 0.18]	-0.84	0.404
Sex	-0.453	0.259	[-0.96, 0.05]	-1.75	0.080†
CRQ	-0.659	0.229	[-1.11, -0.21]	-2.87	0.004**
CRQ × Time[a]	-0.300	0.157	[-0.61, 0.01]	-1.91	0.057†
Model 3c.0 – Dysexecutive behaviors null AIC = 987.6; *W* = 0.012					
CAP	0.317	0.160	[0.004, 0.63]	1.99	0.047*
Time[a]	0.101	0.115	[-0.12, 0.33]	0.88	0.380
Sex	-0.484	0.155	[-0.79, -0.18]	-3.13	0.002**
Model 3c.1 – Dysexecutive behaviors CRQ AIC = 978.8; *W* = 0.988					
CAP	0.161	0.160	[-0.14, 0.47]	1.03	0.302
Time[a]	0.136	0.113	[-0.09, 0.36]	1.21	0.228
Sex	-0.366	0.147	[-0.66, -0.08]	-2.48	0.013*
CRQ	-0.601	0.164	[-0.92, -0.28]	-3.67	<0.001***
CRQ × Time[a]	0.192	0.115	[-0.03, 0.42]	1.67	0.096†
Model 3d.0 – Irritability/aggression null AIC = 808.8; *W* = 0.326					
CAP	0.111	0.282	[-0.44, 0.66]	0.39	0.694
Time[a]	0.029	0.194	[-0.35, 0.41]	0.15	0.883
Sex	-0.416	0.297	[-1.00, 0.17]	-1.40	0.162
Model 3d.1 – Irritability/aggression CRQ AIC = 807.4; *W* = 0.674					
CAP	-0.042	0.280	[-0.59, 0.51]	-0.15	0.881
Time[a]	0.010	0.196	[-0.37, 0.39]	0.05	0.961
Sex	-0.261	0.291	[-0.83, 0.31]	-0.90	0.369
CRQ	-0.642	0.285	[-1.20, -0.08]	-2.25	0.024*
CRQ × Time[a]	-0.145	0.189	[-0.52, 0.23]	-0.77	0.443

Table 3. Individual psychiatric items as independently predicted by CRQ score in combined HD group. All regression estimates are standardized. **P*-values significant at $P<0.05$. ***P*-values significant at $P<0.01$. ****P*-values significant at $P<0.001$. †*P*-values approaching significance. [a]Time in days (accumulative, time at first assessment is zero). AIC=Akaike's information criteria; CAP=standardized CAG-age product[87]; CRQ=Cognitive Reserve Questionnaire[91]; HD=Huntington's disease; *W*=Akaike's information criteria weight[97,98].

Remarkably, in addition to their roles in cognition, these regions concurrently integrate motor and behavioral regulation functions. To start, the interplay between executive functions and sensorimotor processing in the MFG, SMA, and MCC is well known[65–67]. The MCC in particular is regarded as a cognitive node involved in conflict monitoring and action selection and execution, sharing connectivity with both cognitive and motor

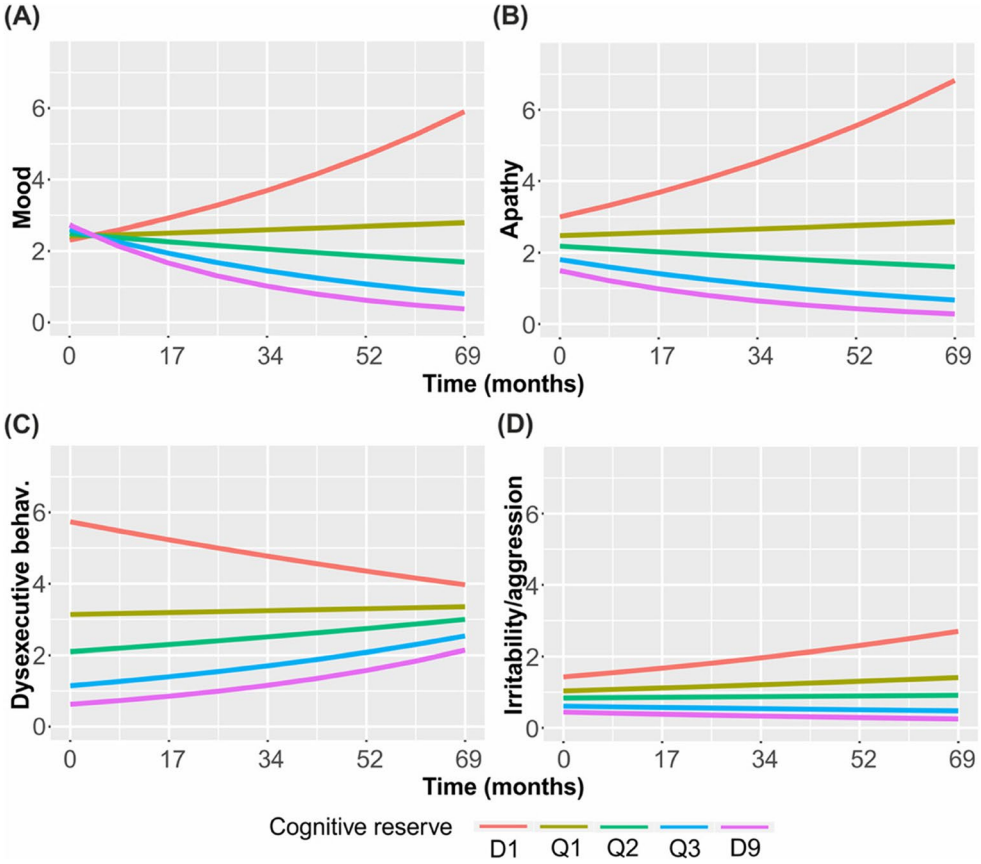

Fig. 3. Higher Cognitive Reserve Questionnaire scores predict lower overall severity across time for psychiatric domains, namely mood (**A**), apathy (**B**), dysexecutive behavior (**C**), and irritability/aggression (**D**). Plots depict the prediction of the different models over time grouped by the different levels (quartiles and deciles) of lifelong cognitive engagement. Image generated with sjPlot package in R v.4.4.0. D1 = first decile; Q1 = first quartile; Q2 = median; Q3 = third quartile; D9 = ninth decile.

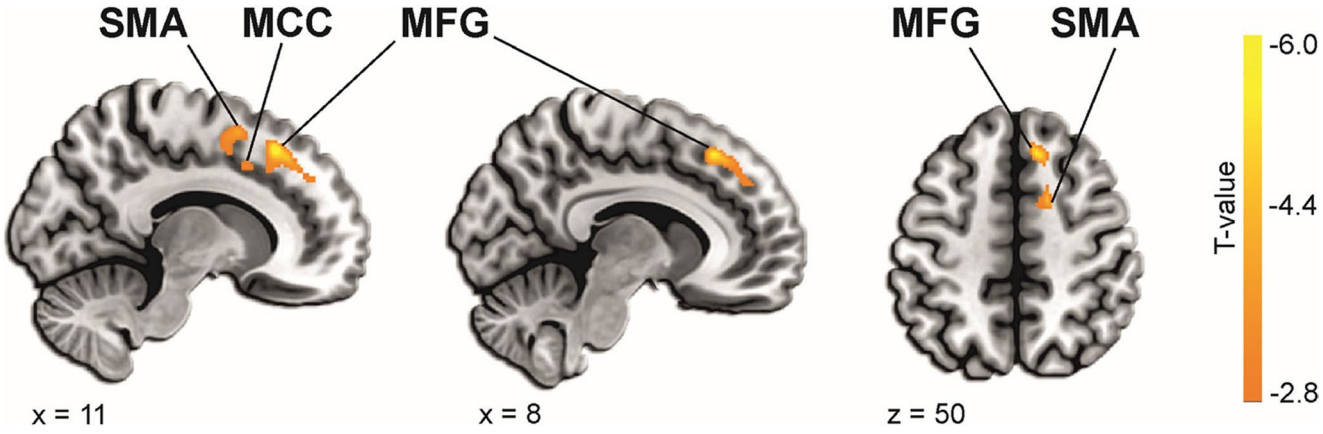

Fig. 4. Longitudinal structural neuroprotection of lifelong cognitive engagement. Higher Cognitive Reserve Questionnaire scores relate with lower gray matter volume atrophy (18 ± 6 months follow-up; cluster size = 100; $P < 0.005$). Slice position labeled in Montreal Neurological Institute coordinates. Significant cluster located in right hemisphere. Image generated with MRIcroGL (v.1.2.20220720; https://www.nitrc.org/projects/mricrogl) and the xjView toolbox (v.10.0; http://www.alivelearn.net/xjview) in SPM12. MCC = middle cingulate cortex; MFG = middle frontal gyrus; SMA = supplementary motor area.

regions[68]. Meanwhile, the SMA serves as an anatomical and functional relay between the primary motor cortex and basal ganglia, playing a role in motor planning and executive control of self-initiated movements, action monitoring, response inhibition, and action sequencing[66]. At the same time, such regions are involved in emotional regulation: decreased connectivity between the SMA and MCC has been associated with increased behavioral apathy[69], the most prevalent psychiatric feature in HD[70], and the MCC has been related with emotional awareness[71]. In summary, converging evidence supports that the MFG, SMA, and MCC act as neural hubs involved in the integration of functionally diverse processes spanning cognitive, motor, and psychiatric domains.

In this vein, our results suggest that these three cortical hubs may collectively serve as a neural basis that, through increased brain maintenance, has the potential to ameliorate cognitive, motor, and psychiatric decline in HD. In the model of resilience, these regions may undergo resistance to degeneration of cortical regions in HD, or possibly simultaneous preservation or enhancement of volume as a consequence of recruitment to sustain clinical functioning.

Recent studies in HD gene-expansion carriers corroborate that lifelong cognitive engagement may confer a protective effect against neurobiological and clinical deterioration, including interactions with genetic modifiers. Specifically, one study demonstrated that intellectual enrichment (i.e., education, pre-morbid intelligence quotient, and occupational cognitive demands) may interact with the *BDNF*gene to putatively counteract negative effects on striatal and whole-brain GMV as well as cognitive function[72]. Moreover, greater intellectual enrichment alone was associated with preserved GMV in the caudate, right putamen, thalamus, and right superior temporal gyrus and ensuing cognitive function in those with low disease burden, an effect which was attenuated as the disease progressed[72]. In a similar vein, the effectiveness of a cognitive compensatory mechanism was represented by a bell-shaped curve in premanifest HD individuals, demonstrating first an increase in effectiveness and a subsequent decrease in the year just prior to predicted disease diagnosis[73]. This corresponded with a similar bell-shaped pattern of hypertrophy of hippocampal GMV and cortical thickness in the left superior parietal cortex[73]. Meanwhile, transgenic mouse models of HD elucidate that a cognitively stimulating environment delays cerebral GMV atrophy as well as age of onset and disease progression[51,52,74], increases brain weight[75], augments dendritic spine density[76], promotes protein recovery[77], and preserves neurogenesis via BDNF[78,79].

The neural areas presented in the current study have also been implicated in brain volume preservation in other populations. For example, healthy individuals with higher levels of education were found to have greater GMV in the anterior cingulate[80]. In behavioral-variant frontotemporal dementia, those with higher physical occupation scores (e.g., more coordination, stamina) demonstrated decreased pathological load in the SMA[81]. In HD specifically, a greater use of bilingualism connoted more executive control and greater GMV in the inferior frontal gyrus, a region involved in the executive control circuit[43], thereby illustrating the interplay between cognitive reserve and brain volume preservation. Meanwhile, among HD patients who were closest to estimated disease onset, a cognitively active lifestyle was related with slower rate of atrophy in the striatum, namely the caudate and putamen[10,39]. While it is important to note that most of the studies are cross-sectional, and thus cannot differentiate between brain reserve and brain maintenance[5], these results substantiate the notion that a cognitively active lifestyle could promote protective mechanisms in both clinical disease expression, neuroprotection, and brain atrophy. Similarly, a recent study demonstrated that lifelong cognitive engagement was significantly related with a modulation of connectivity strength of the MCC (BA 32) and anterior cingulate with the executive control network in HD[10]. Overall, such neuroplastic changes may constitute an intrinsic biological attempt to promote brain maintenance and protection against neurodegeneration, thereby potentiating performance in executive functions.

Of note, we did not identify a relationship between cognitive reserve and GMV atrophy in the striatum, the initial target of neurodegeneration in HD. While a previous longitudinal study does report an association between cognitive reserve and rate of striatal volume loss in premanifest HD[39], our study suggests that brain maintenance at later disease stages may not protect against the primary pathology (e.g., striatal degeneration), but rather via the possible recruitment and subsequent maintenance or even enhancement of brain volume in cortical regions known for their role in functional integration. Additionally, it is also possible that different measures of cognitive reserve, such as premorbid intelligence, education, and occupational status in Bonner-Jackson et al. (2013)[39]vs. lifelong cognitive engagement as measured in the present study (e.g., language learning, musical training, and intellectually stimulating games, among others) may elicit brain maintenance of distinct regions. This underscores the importance of the continued study of cognitive reserve measures as both composite summary proxies and in isolation[5].

The study cohort is relatively small, and neuroimaging analyses were further restricted to a subset; a larger data set could elucidate more nuanced individual differences. For this reason, all participants ($N=45$) with baseline observations were included in the generalized-linear mixed effects model analyses in order to reduce the effect of attrition and improve the precision of intercept estimates (mean length of time between first and final visit of 50.07 ± 17.47 months). Next, despite the regularity of longitudinal visits (mean inter-assessment duration of 13.5 ± 4.1 months), the frequency of data collection could be improved through the use of wearable recording systems[82]. Moreover, the present study focused on the association between lifelong cognitive engagement and longitudinal GMV atrophy. However, due to the fact that neuroimaging data was restricted to 18 months, the present work did not investigate the relationship between neuroimaging data and clinical outcomes in linear mixed models. Finally, because the present study was based on clinical data, there was no control group for comparison. This precluded the assessment of differences between HD gene-expansion carriers and healthy individuals in levels of lifelong cognitive engagement and motor, cognitive, and psychiatric functioning. We were thus unable to evaluate whether the proposed mechanisms pertaining to the relationship between lifelong cognitive engagement and executive processing—and their transfer to other domains—are specific to HD or generalizable to other conditions. Addressing this limitation is an important direction for future research.

When considering the CRQ, one systematic review noted limited content validity of the scale[83], meaning that it does not cover every domain of the construct of cognitive reserve. However, the CRQ has been demonstrated to exhibit good construct validity, structural validity, internal consistency and fair convergent validity[84,85]. Overall, the CRQ has the benefit of evaluating a variety of modifiable aspects related to cognitive reserve.

It is important to note that general intelligence was not investigated in the present study. Past studies have employed different proxies of cognitive reserve, some of which include premorbid intelligence as measured by the National Adult Reading Test (verbal intelligence)[39,86]or subdomains of the Wechsler Abbreviated Scale of Intelligence (vocabulary)[87], either in isolation or together with education. While the present work focused on modifiable factors of lifelong cognitive engagement, it would be worthwhile for future studies to concurrently evaluate the interaction between various factors implicated in cognitive reserve, including intelligence (encompassing various measures of fluid and crystallized intelligence[88]) and other psychosocial contributors (e.g., education, occupation, physical exercise, and engagement in intellectually stimulating leisure activities). This, in turn, may shed light on which factors are most crucial to augmenting the level of cognitive reserve and thereby forestalling brain pathology and clinical progression.

Future work may also pursue other neural mechanisms of plasticity (e.g., white matter, functional connectivity) through which the brain may effectuate changes to better cope with the neurodegenerative process. This point is especially relevant in order to bridge structural imaging studies (i.e., those investigating atrophy, brain reserve, or brain maintenance) with functional studies to identify a network that regulates structural brain status. Additionally, given the apparent impact of lifelong cognitive engagement on non-cognitive symptom domains, future studies may probe the potential mechanisms by which cognitive reserve modulates the interactions between cognitive, motor, and limbic circuits. Other studies are needed to investigate the role of further protective and deleterious lifestyle factors (e.g., physical activity, diet, substance use) on clinical expression and biomarkers of disease progression[50,89], as well as which factors bear the greatest weight on cognitive reserve overall. Moreover, it is important to distinguish lifelong cognitive engagement (e.g., that which is present early in life and measured in the present study) from current cognitive engagement (e.g., continued participation in cognitive and social functions). In this vein, the interplay between cognitive reserve and a recently proposed social reserve is of interest, the latter pertaining to one's social network or social cognition skills[90,91].

In summary, the present findings elucidate the protective benefits that lifelong cognitive engagement beget in terms of not only less severe and slower clinical progression of HD, but also GMV maintenance in functionally connected brain hubs responsible for cognitive, motor, and behavioral integration. As a whole, these results are promising in that they attest to the importance of therapeutic interventions that can promote brain resilience, even, and especially, preceding clinical diagnosis based on motor onset. In the case of HD, preemptive interventions are especially relevant, as premanifest individuals may consider changing their lifestyle habits as a preventive strategy to potentially delay disease progression through both brain maintenance and functional resilience.

An early active cognitive lifestyle may ameliorate symptom severity and progression in motor and psychiatric domains as well as cognitive performance. Such lifestyle factors may confer brain maintenance in hubs known to carry out functional integration, including executive regions that act to integrate action initiation and behavioral regulation. These findings substantiate therapeutic interventions that have the potential to promote brain maintenance and preserved clinical function, even prior to diagnosis.

Methods

Participants

Sociodemographic and clinical information for forty-five HD gene-carriers (≥ 39 CAG repeats) are detailed in Table 4. Despite the fact that HD is clinically defined at motor onset (at which point a patient is diagnosed with manifest HD), actual disease onset occurs gradually[48]. Moreover, neuropathological changes and ensuing cognitive and psychiatric signs can occur before motor symptoms[92–94]. As such, we studied the disease as a continuum of premanifest and manifest individuals. Estimated age of onset for premanifest individuals was calculated utilizing the following model by Langbehn et al. (2010)[15]: 21.54 + Exp(9.556 − 0.146*CAG). Years to onset was calculated as the difference between the estimated age of onset and current age.

Given the progressive nature of the disease and compounding effect of number of CAG repeats, the disease stage can be approximate with the standardized CAG-Age Product (CAP) score, computed as CAP = 100 × age × (CAG – 30) / 627[95]. As such, CAP represents a proxy measure of disease stage that incorporates the length of CAG repeats and age, and can be used to control for individual differences in disease stage among HD gene-carriers.

Participants underwent a baseline clinical evaluation, with successive annual follow-ups constituting a maximum total of six assessments. Generalized linear mixed-effects models included all participants ($N = 45$), with a mean ± standard deviation number of 4.28 ± 1.6 assessments and mean inter-assessment duration of 13.53 ± 4.1 months, resulting in a total of 197 visits (549 observations). The mean ± standard deviation length of time between the first and final visit was 50.07 ± 17.47 (range: 6 to 70 months). In addition, neuroimaging data was collected at baseline with 18 ± 6 months follow-up ($N = 33$). Due to scheduling conflicts, ten participants did not return to complete their second scan. Two participants were claustrophobic and so did not participate in either scan.

The clinical evaluation was carried out by neurologists and neuropsychologists specializing in movement disorders. No participants reported previous history of a neurological disorder other than HD. All individuals provided written informed consent, and ethical approval was granted by the ethics committee of Bellvitge Hospital in accordance with the Helsinki Declaration of 1975. All research was performed in accordance with relevant guidelines and regulations.

	Premanifest	Manifest	HD combined cohort
N	21	24	45
Sex (males/females)	3/18	11/13	14/31
Age (years)	35.71 ± 8.8 (25, 59)	50.21 ± 9.7 (35, 69)	43.44 ± 11.8 (25, 69)
Education	13.33 ± 4.0 (8, 19)	12.08 ± 4.0 (6, 18)	12.67 ± 4.0 (6, 19)
CAP	76.25 ± 16.4 (47.37, 122.01)	107.44 ± 17.6 (73.68, 139.39)	92.89 ± 23.1 (47.37, 139.39)
Estimated age of onset*	47.02 + 8.8 (32.59, 62.64)	–	–
Estimated years to onset†	11.31 ± 8.3 (-8.67, 30.06)	–	–
CRQ	14.38 ± 4.0 (6, 21)	10.88 ± 3.9 (4, 18)	12.51 ± 4.3 (4, 21)
UHDRS-motor	1.30 ± 2.6 (0, 10) *N* = 20	21.17 ± 12.7 (4, 58)	12.14 ± 13.8 (0, 58) *N* = 44
UHDRS-cogscore	134.40 ± 29.8 (100, 200) *N* = 20	77.96 ± 26.9 (21, 117) *N* = 23	104.21 ± 39.9 (21, 200) *N* = 43
F-A-S test	39.30 ± 14.2 (17, 69)	24.09 ± 9.7 (6, 46)	31.12 ± 14.1 (6, 69)
Symbol Digit Modalities	47.55 ± 9.3 (31, 64)	28.17 ± 11.1 (11, 50)	37.19 ± 14.1 (11, 64)
Stroop interference	47.55 ± 13.1 (28, 77)	25.70 ± 10.8 (4, 47)	35.86 ± 16.1 (4, 77)
PBA-s	21.00 ± 25.6 (0, 87)	18.75 ± 16.0 (1, 67)	19.80 ± 20.8 (0, 87)
Mood	8.52 ± 9.7 (0, 28)	4.71 ± 7.9 (0, 34)	6.64 ± 8.9 (0, 34)
Apathy	3.29 ± 5.5 (0, 16)	5.63 ± 5.2 (0, 16)	4.53 ± 5.4 (0, 16)
Irritability/aggression	3.10 ± 6.4 (0, 25)	2.71 ± 4.3 (0, 16)	2.89 ± 5.4 (0, 25)
Psychosis	1.33 ± 3.7 (0, 16)	0.00 ± 0.0 (0, 0)	0.62 ± 2.6 (0, 16)
Dysexecutive behaviors	4.76 ± 8.0 (0, 28)	4.67 ± 4.4 (0, 18)	4.71 ± 6.3 (0, 28)

Table 4. Sociodemographic and clinical information for Huntington's disease gene-carriers at baseline. Data presented as *mean ± standard deviation (minimum, maximum)*. *N*(number of participants) detailed in individual cells when differing. Premanifest and manifest categories designated based on Unified Huntington's Disease Rating Scale diagnostic confidence score for motor abnormalities at first visit[101]. * Estimated age of onset based on model by Langbehn et al. (2010)[15]. † Estimated years to onset calculated as difference between estimated age of onset and current age. CAP=standardized CAG-age product[87]; CRQ=Cognitive Reserve Questionnaire[91]; HD = Huntington's disease; *N*=number of participants; UHDRS-cogscore=Unified Huntington's Disease Rating Scale total cognitive score[102]; UHDRS-motor=Unified Huntington's Disease Rating Scale total motor score; PBA-s=short-Problem Behavior Assessment[89].

Clinical evaluation

In order to assess cognitive performance in the present sample, the Unified Huntington's Disease Rating Scale total cognitive score (UHDRS-cogscore) was employed to evaluate phonetic verbal fluency (F-A-S test), psychomotor speed (Symbol Digit Modalities Test), and processing speed, attention, and inhibitory control (word-reading, color-naming, and interference components of the Stroop Test).

To evaluate motor symptomatology, we employed the UHDRS Total Motor Score (UHDRS-motor), which includes dysarthria, chorea, dystonia, gait, postural stability, and oculomotor function[96].

Neuropsychiatric features were evaluated using the short-Problem Behavior Assessment (PBA-s)[97]. This semi-structured interview is administered in the presence of a knowledgeable informant. Psychiatric domains comprise five composite scores, as follows: mood (depression, suicidal ideation, anxiety), apathy, irritability/aggression (irritability, angry or aggressive behavior), dysexecutive behaviors (preservative thinking/behavior, obsessive–compulsive behavior), and paranoia (paranoid thinking/behavior, hallucinations)[98].

A lower UHDRS-cogscore, in contrast to higher UHDRS-motor and PBA-s scores, represents worse functioning.

Lastly, the Cognitive Reserve Questionnaire (CRQ)[99]was administered at baseline as a proxy measure of lifelong cognitive engagement. The CRQ includes eight items: education (years), parental education (years), occupation, training courses, musical training, number of spoken languages, reading activities, and frequency of involvement in intellectual games. The questionnaire has a maximum score of 25, representing the highest level of measured cognitive reserve. As such, the CRQ has the benefit of evaluating a variety of modifiable aspects related to cognitive reserve. Furthermore, this questionnaire has been validated in the Spanish speaking population in both healthy elderly and those with Alzheimer's disease[85,99], and has since been implemented in Parkinson's disease[100]and young adults[101]. Moreover, the CRQ correlates with performance on executive functions[99], which are prominent cognitive functions impaired in HD, and has been previously implemented in the HD gene-expansion carrier population in a recent cross-sectional study[10]. Given the above reasons, the CRQ was selected for the present study.

MRI data acquisition and processing

MRI data were acquired through the same 3T whole-body MRI scanner (Siemens Magnetom Trio; Hospital Clinic, Barcelona), using a 32-channel phased array head coil using the same acquisition protocol for all participants. Specifically, structural images comprised a conventional high-resolution 3D T1 image (MPRAGE

sequence), 208 sagittal slices, repetition time = 1970ms, echo time = 2.34ms, inversion time = 1050ms, flip angle = 9°, field of view = 256 mm, 1 mm isotropic voxel with no gap between slices.

Statistical analysis

Statistical analyses of group demographics were performed in SPSS (v.25; SPSS Inc., Chicago, IL).

Generalized linear mixed-effects models

In order to study whether the CRQ score was predictive of individual differences in longitudinal symptom development across cognitive, motor, and psychiatric domains, general linear mixed-effects models were implemented in R (v4.4.0, R Foundation for Statistical Computing, Vienna, Austria). Generalized linear mixed-effects models provide flexibility in the evaluation of subject-specific trends in longitudinal analysis[102,103], and have previously been implemented in the study of HD[20,39,104].

The analytic strategy comprised three independent sets of nested models, with the respective outcome (dependent) variables being UHDRS-cogscore, UHDRS-motor, or PBA-s scores, respectively (maximum of six values per clinical variable). For each set of models, the null model only included the variables of time in days (accumulative, from the first to the final visit), as well as the control variables of sex and CAP, the latter controlling for disease stage (including age and CAG repeats). Sex was coded as 0 (male) and 1 (female). Meanwhile, the alternative model additionally included the main predictor variable of interest, CRQ, with an interaction term between CRQ and time. Subject-specific random effects were specified for baseline (intercept), and random slopes were modeled for time. (See Supplementary Materials for details and analysis code.)

Goodness of fit of the two models was evaluated using the likelihood ratio test along with a probability scaling of Akaike's information criteria weight (W). The criteria represent the relative likelihood, or quality, of the statistical model. Wvalues are considered a global relative effect size measure[105,106] and range from 0 to 1 (closer to 1 indicating better relative fit). P-values significant at $P < 0.05$ for each model.

The above analytic strategy was extended to assess how CRQ scores predict individual performance of the three cognitive subdomains comprising the UHDRS-cogscore separately, namely the F-A-S test, Symbol Digit Modalities Test, and Stroop interference, using three sets of nested models as above. This was again repeated for the four subdomains of the PBA-s (mood, apathy, irritability/aggression, and dysexecutive behaviors) this time with four sets of nested models. Due to a high proportion of zero values (91.62%), the psychosis domain was excluded from the analysis. Finally, exploratory analyses were performed to consider the effects of all above models in manifest and premanifest groups separately.

Longitudinal voxel-based morphometry (VBM) of T1-weighted images

Morphometric analysis was implemented using the CAT12 toolbox longitudinal processing pipeline (http://dbm.neuro.uni-jena.de/cat/) in SPM12 (Welcome Department of Imaging Neuroscience Group, London, UK) running on MATLAB (v19.b, Mathworks, Natick, MA). Preprocessing, realignment, segmentation, normalization, and smoothing followed the same protocol as De Paepe et al. (2020)[104].

Specifically, preprocessing for the longitudinal data considered the characteristics of intra-subject analysis by the registration of the second image to the baseline image, and a subject-specific mean image was created from the realigned images and used as a reference for the realignment of both time points. Realigned images were segmented, corrected for signal inhomogeneity, and normalized using the Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm (DARTEL). Then, the corresponding normalization parameters were applied to the segmented gray matter images of both time points. Resulting gray matter normalized images were modulated by their Jacobian determinants and spatially smoothed (full width at half maximum = 8 mm), allowing direct comparison of regional differences in GMV[108]. Images were then visually inspected.

Finally, smoothed GMV difference maps between the two time points were calculated for each participant. These images were entered into a linear regression analysis model in SPM12 in order to investigate the association between CRQ scores and changes in GMV at the whole-brain level. Time between scans (days), CAP scores, total intracranial volume (sum of gray matter, white matter, and cerebrospinal fluid, averaged across both sessions), and sex served as control variables.

Significant results were first identified at $P < 0.005$ at voxel-level (uncorrected) with a minimum cluster size of 100 contiguous voxels. Multiple comparisons were corrected for at a threshold of $P < 0.05$ applied at cluster-level. Suprathreshold maxima were localized through rendering onto a normalized T1 structural Montreal Neurological Institute (MNI) reference brain.

Data availability

The raw data supporting the findings of this study cannot be shared publicly as they contain clinical and genetic information sensitive to the Institution. In the interest of minimizing the risk of participant identification, we will make the data available upon reasonable request to the corresponding author (email: ecamara@idibell.cat), with approval by the local institutional review board.

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Author contributions

AdP executed the study, performed analysis, wrote the manuscript, and edited the final version. YPA executed the study, performed analysis, and wrote the manuscript. CGG, NRD, IV, and MC executed the study and edited the final version of the manuscript. RdB designed the study and edited the final version of the manuscript. EC designed the study, executed the study, performed analysis, and edited the final version of the manuscript. All authors reviewed the manuscript. AdP: Audrey E De Paepe; YPA: Yemila Plana-Alcaide; CGG: Clara Garcia-Gorro; NRD: Nadia Rodriguez-Dechicha; IV: Irene Vaquer; MC: Matilde Calopa; RdD: Ruth de Diego-Balaguer; EC: Estela Camara.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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