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An active cognitive lifestyle as a potential neuroprotective factor in Huntington's disease

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ABSTRACT

A cognitive stimulating lifestyle has been observed to confer cognitive benefits in multiple neurodegenerative diseases. However, the underlying neurobiological basis of this phenomenon remains unclear. Huntington's disease can provide a suitable model to study the effects and neural mechanisms of cognitive engagement in neurodegeneration. In this study, we investigate the effect of lifestyle factors such as education, occupation and engagement in cognitive activities in Huntington's disease gene carriers on cognitive performance and age of onset as well as the underlying neural changes sustaining these effects, measured by magnetic resonance imaging. Specifically, we analyzed both gray matter volume and the strength of connectivity of the executive control resting-state network. High levels of cognitive engagement were significantly associated with more preserved executive functions, a delay in the appearance of symptoms, reduced volume loss of the left precuneus and the bilateral caudate and a modulation of connectivity strength of anterior cingulate cortex and left angular gyrus with the executive control network. These findings suggest that a cognitively stimulating lifestyle may promote brain maintenance by modulating the executive control resting-state network and conferring protection against neurodegeneration, which results in a delayed onset of symptoms and improved performance in executive functions.

1. Introduction

Studies on aging and dementia suggest that lifelong experiences, including education, occupational attainment and leisure activities can minimize cognitive decline (Andrejeva et al., 2016; Fratiglioni and Wang, 2007; Fritsch et al., 2002; Hindle et al., 2014; Serra et al., 2015; Stern, 2002; Sumowski et al., 2013).

Despite the relevance of the potential positive impact of an intellectually stimulating lifestyle (i.e. cognitive engagement) on neurodegeneration-related symptoms, the neural mechanisms underlying its

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effects remain controversial. Whether a cognitively active lifestyle provides a higher tolerance to neurodegeneration (resilience) or whether it slows the neurodegenerative process itself (resistance) is still not clear. The nomenclature of resistance and resilience has been recently proposed (Arenaza-Urquijo and Vemuri, 2018) as an alternative to a variety of terms such as cognitive reserve (Stern, 2009, 2002), brain reserve (Satz, 1993; Stern, 2009), brain maintenance (Nyberg et al., 2012), neuroprotection (Milgram et al., 2006; Nithianantharajah and Hannan, 2011) and neural compensation (Scheller et al., 2014; Stern, 2009) with the aim of finding a simplified and unified framework. Previous studies on Alzheimer's disease have reported intact cognitive functioning among patients with higher levels of education despite the severity of the neuropathology (Roe et al., 2007). This would indicate that cognitive engagement, that is, the level of cognitive activity throughout life, does not provide protection from neurodegeneration itself, rather from the cognitive symptoms that result from this degeneration, conferring resilience but not resistance. On the other hand, in individuals at risk of Alzheimer's disease, higher levels of engagement in cognitively stimulating activities was associated not only with better cognitive performance but also with greater grey matter volume in areas particularly vulnerable in this disease (Schultz et al., 2015). This would suggest some level of resistance to neurodegeneration. A cognitively active lifestyle has also been associated with changes in both brain activity and resting-state functional connectivity in normal aging (Bastin et al., 2012; Marques et al., 2015) and Alzheimer's disease (Bosch et al., 2010; Bozzali et al., 2015; Franzmeier et al., 2017a; Schultz et al., 2015; Solé-Padullés et al., 2009). Furthermore, in Alzheimer's disease, global functional connectivity in the left prefrontal cortex has been associated with both more years of education (Franzmeier et al., 2017b) and more preserved cognitive function (Franzmeier et al., 2018).

Huntington's disease can provide a suitable model to study the effects of cognitive engagement on neurodegenerative processes from its early stages. Huntington's disease is a neurodegenerative genetic disorder caused by an expansion of a CAG repeat in the *HTT* gene (Gusella et al., 1983). It shares many features, such as delayed onset, selective neuronal vulnerability, protein aggregation and propagation of the aggregates between cells, with other more common neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (Flavin et al., 2017; Ross and Tabrizi, 2011). However, it has the particularity that individuals who will develop the disease can be identified before clinical onset by predictive genetic testing. This makes it possible to study the neurodegenerative process before clinical signs appear. Furthermore, Huntington's disease also allows us to study the effects of cognitive engagement on delaying the onset of clinical symptoms at the individual level, since it is possible to calculate the theoretical age of onset of a given Huntington's disease mutation carrier on the basis of the genetic information. It is known that the size of the CAG repeat sequence is inversely related to the age of motor onset and affects the evolution of motor, cognitive and functional symptoms (Langbehn et al., 2010; Rosenblatt et al., 2012; Trottier et al., 1994). However, the CAG repeat length only accounts for approximately 56% of the variation in the age of onset (Gusella et al., 2014). Modulatory genes and life experiences are thought to play a role in the heterogeneity observed in the appearance of the first clinical symptoms (de Diego-Balaguer et al., 2016; Nithianantharajah et al., 2009). In this regard, cognitive engagement could be a possible mediator in the age of onset.

Studies done in murine models of Huntington's disease have shown that enriched environments delay the onset of motor symptoms (Hockly et al., 2002; Pang et al., 2006; van Dellen et al., 2000) and have beneficial effects on cognitive (Curtin et al., 2015; Nithianantharajah et al., 2009; Pang et al., 2006; Wood et al., 2011) and motor performance (Schilling et al., 2004). Moreover, studies on humans have shown that a cognitively active lifestyle has a beneficial effect on clinical symptoms in Huntington's disease (Bonner-Jackson et al., 2013; Trembath et al., 2010). However, the effects of high cognitive engagement on the age of onset are controversial (López-Sendón et al., 2011; Trembath et al., 2010).

A slower volume loss in caudate and putamen has been reported in those premanifest Huntington's disease individuals with higher cognitively active lifestyle, computed on the basis of premorbid intellectual level, occupation and education (Bonner-Jackson et al., 2013). This study suggested that the level of cognitive engagement can modulate brain resistance in Huntington's disease regarding grey matter volume. However, the effects of cognitive engagement on brain function have not been studied in Huntington's disease.

In the current study, we have investigated the effect of current and lifelong cognitive engagement on the age of onset and cognitive symptoms in Huntington's disease patients. We focused on executive functions, since these are the earliest signs of cognitive impairment in Huntington's disease (Larsen et al., 2015). In addition, we examined the effect of cognitive engagement on the brain, by analyzing MRI measures of grey matter volume and functional connectivity in the executive control resting-state network (EC-RSN) (Smith et al., 2009), a well-defined network that comprises medial-prefrontal areas commonly found to be involved in executive functions. Strength of connectivity within this network has been associated with performance levels in executive functions tests in healthy subjects (Seeley et al., 2007) and individuals with mild cognitive impairment (Wu et al., 2014a). Furthermore, the EC-RSN has been found to be altered in those patients (Werner et al., 2014; Wolf et al., 2014). We hypothesized that a more cognitively active lifestyle in Huntington's disease patients would be associated with a delayed age of onset, less severe impairment of executive functions, differences in the functional connectivity of the EC-RSN, and more preserved gray matter volume.

2. Materials and methods

2.1. Participants

Thirty-two Huntington's disease gene-carriers (31.3% males; age: M = 46.16, SD = 12.39) at different stages of the disease were tested. In order to reliably define the EC-RSN, 30 controls (45.2% males; age: M =45.80, SD = 10.21) matched for age ($t(60) = 0.008$, $p = 0.9$ two-tailed) and years of education ($t(60) = -1,27$, $p = 0.2$, two-tailed) were also included. Huntington's disease individuals were defined as carriers of the genetic mutation with ≥ 36 repeats. Twenty-one of the gene-carriers were manifest Huntington's disease patients, defined as those gene-carriers with a diagnostic confidence score of four on the UHDRS (Huntington Study Group Investigators, 1996), which corresponds to a confidence of ≥ 99% that the motor abnormalities are due to Huntington's disease. Eleven of the gene-carriers were premanifest Huntington's disease individuals, defined as carriers of the genetic mutation with a Disease Confidence Score (DCS) of less than four. From the 11 premanifest individuals, six of them presented cognitive or psychiatric symptoms. We studied the disease as a continuum since the dichotomy between premanifest and manifest individuals is somewhat artificial (Ross et al., 2014) as it is based solely on the basis of motor dysfunction. Despite the fact disease onset is clinically set when motor signs appear, actual disease onset is a process that occurs gradually and cognitive and psychiatric disturbances can occur before motor signs appear. Gene-carriers clinical characteristics are detailed in Table 1. We controlled for individual differences among Huntington's disease gene carriers in the expected burden of the disease given their age and CAG repeat length by using the Disease Burden score as a nuisance variable. This score is computed as: Disease Burden = age x (CAG −35.5) (Penney et al., 1997). None of the patients or controls reported previous history of neurological disorder other than Huntington's in the case of the patients. All participants gave informed consent to participate in this study. Ethical approval for the study was granted by the ethics committee of Bellvitge Hospital.

Table 1
Demographic, clinical and neuropsychological information for Huntington's disease gene carriers.

	N	Mean (*SD*)
Age	32	46.16 (12.39)
Sex (% male)	32	31.3
Education (years)	32	11.69 (2.89)
CAG	32	44.28 (3.13)
Disease Burden	32	383.08 (112.94)
Theoretical AOO (Langbhen)	32	45.74 (10.27)
Theoretical AOO (Gutierrez)	32	41.57 (9.95)
AOO	23[a]	41.70 (10.48)
DAT	23[a]	3.62 (8.59)
Motor UHDRS	32	14.03 (11.98)
Cognitive UHDRS	30	231.87 (73.58)
TFC	32	12.06 (1.32)
CRQ	31	11.77 (4.01)
Stroop interference	30	3.93 (10.42)
Backward digit span	30	3.53 (1.07)
Trail Making Test B-A	28	84.32 (56.33)

AOO = Age of Onset; CRQ = Cognitive Reserve Questionnaire; DAT = Difference Actual Age of Onset – Theoretical Age of Onset; TFC = Total Functional Capacity; UHDRS = Unified Huntington's Disease Rating Scale.
[a] Only individuals who report having symptoms.

2.2. Clinical evaluation

All patients were evaluated using the Unified Huntington's Disease Rating Scale (UHDRS) (which comprises Motor, Cognitive and Behavioral subscales) as well as additional executive functions tests: measures of inhibition (Stroop color word interference (Golden, 1978)), working memory (backward digit span (Wechsler, 1997)), phonemic fluency (verbal letter fluency test (FAS) (Butters et al., 1986)) and cognitive flexibility (Trail Making Test B-A difference score (TMT B-A) (Tombaugh, 2004)).

For some participants, due to timing constrains, not all tests could be administered. The specific *N* for each test is detailed in Table 1.

2.3. Cognitive engagement evaluation

Participants completed the Cognitive Reserve Questionnaire (CRQ) (Rami et al., 2011) as a proxy measure of current and lifelong cognitive engagement. The CRQ includes eight items and provides information regarding years of education, years of parent's education, type of occupation, number of training courses completed, musical training, number of spoken languages, reading activity and frequency of involvement in intellectual games. The questionnaire has a maximum score of 25, with 25 representing the highest level of cognitive engagement.

2.4. Age of onset

2.4.1. Theoretical age of onset

We used the models proposed by Langbehn et al. (2004) (21.54 + Exp (9.556–0146*CAG) and Gutierrez and MacDonald (Guitierrez and MacDonald, 2002) (48.1685–0.376508* CAG)/(−1.49681 + 0,051744*CAG) to predict the theoretical age of onset in each individual, which is defined on the basis of motor signs.

2.4.2. Age of onset

In order to cover the multidimensional spectrum of Huntington's disease and be able to evaluate initial symptoms even in premanifest individuals, we considered the age of onset as the age at which the first symptom of any of the three domains (motor, psychiatric or cognitive) appeared. Specifically, we devised a questionnaire which was answered by the main caregiver or the closest relative of each gene-carrier. In those cases where the relatives were not confident about their report regarding the age of onset, which occurred with three patients, this was retrospectively estimated by the patient's reference clinician.

2.4.3. Difference between actual and theoretical age of onset

The difference between actual and theoretical age of onset was calculated for each patient (DAT = Actual age of onset – Theoretical age of onset). Thus, a positive number in the difference indicates a delay in the appearance of the clinical symptoms, whereas a negative number indicates an earlier onset than that predicted theoretically.

2.5. MRI data acquisition

MRI data were acquired through a 3 T whole-body MRI scanner (Siemens Magnetom Trio; Hospital Clínic, Barcelona), using a 32-channel phased array head coil. Structural images comprised a conventional high-resolution 3D T1 image (MPRAGE sequence), 208 sagittal slices, TR = 1970 ms, TE = 2.34 ms, TI = 1050 ms, flip angle = 9°, FOV = 256 mm, 1 mm isotropic voxel). Functional data (resting-state fMRI) were acquired with a gradient echo-planar imaging sequence (150 volumes, 30 axial slices; 3 mm in-plane resolution, 4 mm thickness, no gap, TR = 2000 ms; TE = 29 ms; flip angle = 80°; FOV = 256 mm).

2.6. MRI preprocessing

2.6.1. Resting-state functional connectivity

Independent Component Analysis (ICA) was used to detect spatially independent and temporally coherent patterns of functional brain connectivity in the EC-RSN by using Multivariate Exploratory Linear Decomposition into Independent Components and dual regression analysis (Filippini et al., 2009; Smith et al., 2009; Zuo et al., 2010), both algorithms implemented in FSL (www.fmrib.ox.ac.uk/fsl) following the standard protocol. The preprocessing of the data included brain extraction, motion correction, spatial smoothing (FWHM 6 mm) and high-pass temporal filtering. To control for potential motion confounds, the head motion parameter was computed for each participant as the average root mean square of displacements. This parameter was computed with MCFLIRT at the motion correction stage during preprocessing (Jenkinson et al., 2002) and was averaged over all volumes to obtain a single measure of head motion per participant.

Normalized data of all participants, combining patients and healthy controls, were temporally concatenated into a 4D time series and then decomposed into spatially independent maps using ICA and constrained to 25 components (Beckmann and Smith, 2004; Smith and Nichols, 2009). All ICA maps were spatially regressed against the individual resting-state data set and then the resulting time-courses were entered into a second regression analysis that allowed the estimation of the spatial component maps for each individual in terms of voxel-wise z-scores.

Next, we visually selected the ICA component maps that showed a close correspondence to our network of interest, the EC-RSN (Figure 1 and Table 2), identifying it as the group ICA component that showed highest spatial correlation ($r > 0.4$) with the EC-RSN template from the study by Smith et al. (2009).

2.6.2. Voxel-based morphometry of T1-weighted images

A morphometric analysis was carried out using the vbm8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) in the SPM8 software package (Welcome Department of Imaging Neuroscience Group, London, UK) running on MATLAB (v12.b, Mathworks, Natick, MA). During the segmentation step, spatial regularization (regularization: 0.02, discrete cosine transform warp frequency cutoff of 22) was adapted to account for striatal neurodegeneration and ventricle dilatation. The resulting gray matter normalized images were modulated by their Jacobian determinants and spatially smoothed (FHWN = 8 mm), which allow direct comparison of regional differences in the volume of gray matter

Table 2
Executive control resting-state network functional connectivity for controls and Huntington's disease gene carriers ($p < 0.05$ FWE-corrected at whole brain level, cluster extent > 20 voxels).

Anatomical region	Cluster size (voxels)	MNI coordinates (x y z)	*t* value
Positive effects			
ACC	2625	− 2 30 32	16.84
L DLPFC		− 34 34 36	14.39
MCC		6 14 44	14.15
R DLPFC		34 42 36	11.91
SMA		14 10 60	11.56
L PMC		18 14 52	9.94
R PMC		− 18 10 56	9.5
R Ains		34 18 8	7.13
R SMG	158	58 − 38 32	12.67
L SMG	168	− 62 − 38 32	11.28
L aINS	115	− 46 18 − 4	9.35
Negative effects			
L AngG/ IPL	139	− 38 − 74 48	9.93
R AngG /IPL	71	50 − 66 40	7.82

MNI = Montreal Neurological Institute stereotactic space; ACC= Anterior Cingulate Cortex; DLPFC= Dorsolateral Prefrontal Cortex; MCC = Middle Cingulate Cortex; SMA = Supplementary Motor Area; PMC = Premotor Cortex; aINS = anterior Insula; SMG = Supra Marginal Gyrus; AngG = Angular Gyrus; IPL = Inferior Parietal Lobe; R = Right; L = left. Cluster size is reported in those MNI coordinates of the largest peak within each cluster.

(Mechelli et al., 2005).

2.7. Statistical analysis

2.7.1. Behavioral data analysis

Statistical analysis was performed using SPSS 21.0 software (SPSS Inc, Chicago, USA). Correlation analyses were conducted to investigate possible relationships between CRQ scores and the different executive functions variables, as well as between CRQ scores and the DAT. The normality of the distribution of the different variables was assessed graphically (histogram and Q-Q plot) and through the Shapiro-Wilk test ($n < 50$). We used Pearson's correlation coefficients in those scores that were normally distributed. For not normally distributed scores, Spearman's correlation coefficients were calculated. In the latter case, this is specified in the manuscript. Moreover, when indicated, the correlation analyses were adjusted for Disease Burden in order to control for the variability between Huntington's disease patients associated with the load of the disease. A separate adjustment for age was not performed since Disease Burden score already includes age. Differences were considered statistically significant when *p*-values were $p < 0.05$.

2.7.2. Neuroimaging data analysis

For the resting-state fMRI data, the group-level EC-RSN map was identified using a one-sample *t*-test (including both positive and negative effects) after entering the individual EC-RSN maps for both the Huntington's disease patients and controls. Moreover, regression analysis within a linear model was applied for the CRQ scores and the EC-RSN images masked with the group-level EC-RSN map, including Disease Burden as a nuisance variable. For the morphometry data, a regression analysis within a linear model was applied for the CRQ scores and the smoothed gray matter volume images, including Disease Burden as a nuisance variable in the model.

In order to define the group level EC-RSN connectivity map, results were reported using a threshold of $p < 0.05$ with FWE correction for multiple comparisons at whole-brain level. Linear correlations between CRQ scores and both morphometry and EC-RSN data were identified at $p < 0.005$ uncorrected and a threshold of $p < 0.05$ was applied at cluster level using an FDR correction, with a minimum cluster size of 20 (EC-RSN data) and 50 (morphometry data) contiguous voxels. The maxima of suprathreshold regions were localized by rendering them onto a normalized T1 structural MNI reference brain.

Finally, we wanted to investigate the relationship between brain measures and performance in executive functions in those regions modulated by CRQ scores. Based on the results of the regression analyses both in the case of EC-RSN and VBM maps, post-hoc partial correlation analyses were performed between a composite measure of executive performance and mean neuroimaging values (functional connectivity strength and grey matter volume, respectively) in those regions where significant correlations with CRQ scores had been found. By including this as a nuisance variable, we eliminated the effect of CRQ scores. The composite measure of performance in executive functions for each participant was the factor score of the first component of a principal component analysis (PCA) including all the different measures of executive performance standardized.

3. Results

3.1. Behavioral data

3.1.1. Relationship between cognitive engagement and neuropsychological data

The performance in executive functions was significantly influenced by the level of cognitive engagement in Huntington's disease gene carriers. Individuals with higher CRQ scores showed better performance in working memory (backward digits span ($r = 0.64$; $p = 0.004$)), inhibitory control (Stroop color word interference ($r = 0.44$; $p = 0.055$)) and cognitive flexibility (TMT B-A ($r = -0.48$; $p = 0.030$)), controlling by Disease Burden and adjusting for multiple comparisons by FDR correction (adjusted *p* values) (Fig. 1A). No significant correlation was found with verbal fluency. A correlation analysis was performed between age and CRQ scores to assess a potential confounding effect of age. Importantly, no significant effect was observed ($p = 0.268$).

3.1.2. Impact of cognitive engagement on age of onset

Importantly, we found a significant positive correlation between CRQ scores and the difference between actual and theoretical age of onset (DAT) for both models of theoretical age of onset (Langbhen: Spearman correlation, $r_s = 0.48$, $p = 0.025$; Gutierrez: Spearman correlation $r_s = 0.47$; $p = 0.024$). Thus, the effect of cognitive engagement was reflected in a delay in the appearance of the first clinical symptoms in those patients with higher CRQ scores and an advance in those patients with lower CRQ scores (Fig. 1B).

3.2. Neuroimaging data

3.2.1. Executive control resting-state network

The group-level EC-RSN map of Huntington's disease patients and controls is shown in Fig. 2. The areas with a positive coupling corresponded to regions typically found in the literature as part of the EC-RSN: the anterior cingulate cortex (ACC) and the medial cingulate cortex (MCC) bilaterally, the dorsolateral prefrontal cortex (DLPFC), the premotor cortex, the supplementary motor area (SMA), the anterior insula and the supramarginal gyrus. The only region that showed a negative coupling was the inferior parietal lobe (IPL) bilaterally, including the angular gyrus (AngG) (Table 2).

3.2.2. Cognitive engagement effects in the executive control resting-sate network

In Huntington's disease patients, CRQ scores correlated negatively with the EC-RSN connectivity strength in the ACC (x = 6, y = 14, z = 32, *t*-value = 4.38, $p = 0.035$ at cluster level (FDR-corrected)) and positively in the left AngG (x = −38, y = −70, z = 48, *t*-value = 5.26, $p = 0.029$ at cluster level (FDR-corrected)) (Fig. 3A). In the case of the

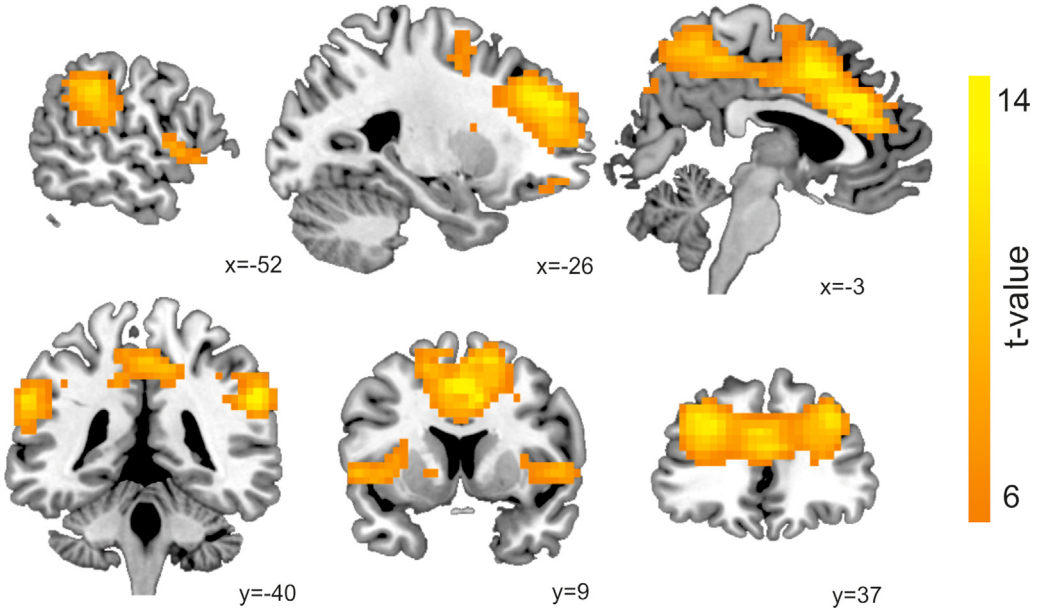

Fig. 1. Executive control resting-state network (EC-RSN) in controls and Huntington's disease gene carriers. The EC-RSN is overlaid on a high resolution structural MNI template.

AngG, since this area showed a negative connectivity strength with the EC-RSN, a positive correlation meant that higher CRQ scores were associated with less negative strength connectivity. Thus, in both regions, cognitive engagement was associated with less connectivity strength.

3.2.3. Association between functional connectivity and executive functions

After investigating the relationship between cognitive engagement and functional connectivity, we wondered whether this reduction in functional connectivity in the ACC and the AngG associated with higher cognitive engagement would be also associated with better cognitive performance. In order to clarify this, we carried out a partial correlation analysis between executive performance and functional connectivity strength in those regions whose connectivity strength significantly correlated with CRQ scores, namely the ACC and the left AngG. We removed the effects of cognitive engagement by including CRQ scores as a nuisance variable so that the effects could not be explained by shared variance with this measure. We did not find significant correlations between functional connectivity strength and performance in executive functions.

3.2.4. Cognitive engagement effects in gray matter volume

We found that CRQ scores positively correlated with measures of gray matter volume obtained using voxel-based morphometry. In particular, higher cognitive engagement levels were significantly associated with a lower loss of gray matter in the precuneus (Left, x = −20, y = −48, z = 45, *t*-value = 5.13, $p = 0.034$ at cluster level (FDR-corrected); Right, x = 2, y = −52, z = 48, *t*-value = 4.66, $p = 0.017$ at cluster level (FDR-corrected)). Moreover, a significant correlation with CRQ scores was also observed in the volume of the caudate bilaterally after small volume correction (Right, x = 15, y = 9, z = 21, *t*-value = 3.07; left, x = −14, y = 9, z = 21, *t*-value = 3.17) (Fig. 3B).

3.2.5. Association between grey matter volume and executive functions

After finding that higher cognitive engagement was associated with more preserved grey matter volume in precuneus and caudate, we tested whether a greater volume in those regions was also associated with better performance in executive functions after removing the effect of CRQ scores. In this case, we found significant correlations between performance and higher volume in all four regions (FDR-corrected): left precuneus ($r = 0.55, p = 0.004$), right precuneus ($r = 0.58, p = 0.003$), left caudate ($r = 0.62, p = 0.003$) and right caudate ($r = 0.59, p = 0.003$) (adjusted *p* values).

4. Discussion

The present study investigates the impact of the levels of current

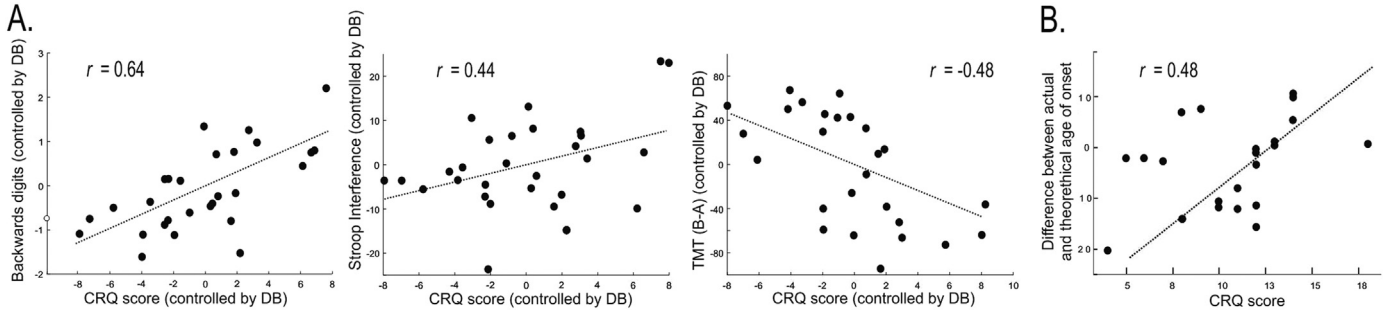

Fig. 2. Association of cognitive engagement with cognitive performance and age of onset. A) Scatter plot of the correlation analysis between CRQ scores and better performance in working memory (backward digits), inhibitory control (Stroop color word interference) and cognitive flexibility (TMT B-A) controlling by Disease Burden. B) Scatter plot of the correlation analysis between CRQ scores and difference between actual and theoretical age of onset (DAT) calculated from the Langbhen equation. A positive number in the DAT indicates a delay in the appearance of the clinical symptoms, whereas a negative number indicates an earlier onset than theoretically expected. CRQ = Cognitive Reserve Questionnaire; DB = Disease Burden; TMT = Trail Making Test.

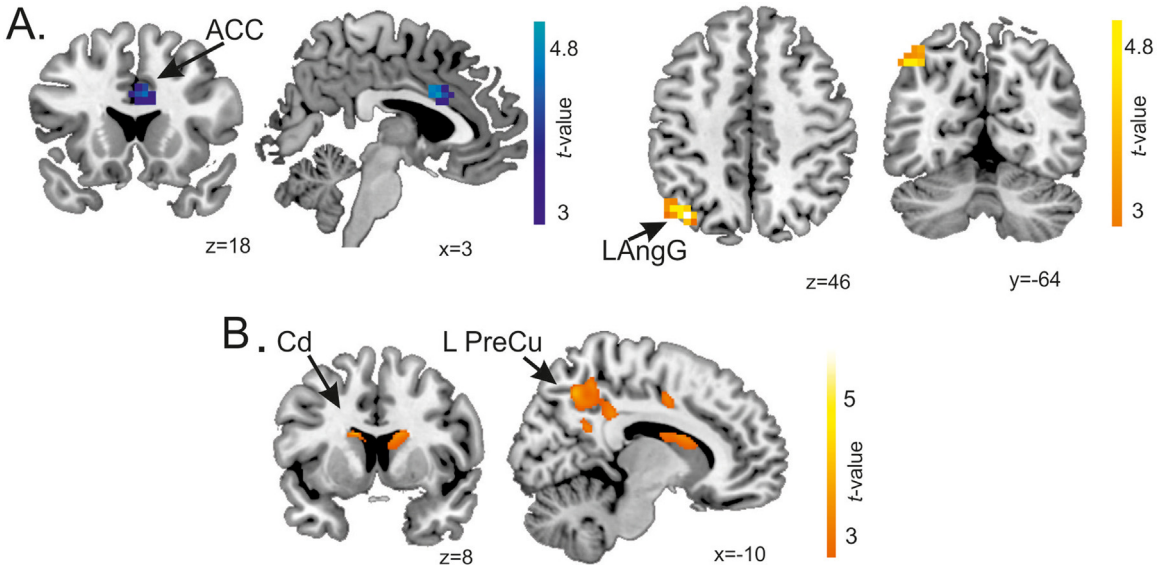

Fig. 3. Functional and structural modulations of cognitive engagement in Huntington's disease patients. A) Significant correlations between CRQ and functional connectivity strength in the executive control network. Hot colors represent positive significant regions and cold colors represent negative correlations, overlaid on an MNI template. B) Results of the voxel-based morphometry analysis of the structural T1-weighted images. The slices show regions of greater gray matter volume associated with higher CR scores, overlaid on a structural MNI template. ACC = Anterior Cingulate Cortex; L AngG = Left Angular Gyrus; Cd = Caudate; L PreCu = Left Precuneus.

and lifelong cognitive engagement on the modulation of age of onset, cognitive performance and brain function and structure in Huntington's disease carriers. Our findings provide converging evidence that higher levels of cognitive engagement are associated with the delayed appearance of Huntington's disease symptoms and less severe cognitive deficits. Furthermore, our results suggest that a cognitively active lifestyle is associated with higher structural brain resistance against neurodegeneration and reduced functional connectivity. Importantly, CRQ scores were not significantly associated with age. Furthermore, we removed the effect of age by controlling for Disease Burden. Therefore, our results showing the positive effects of high levels of cognitive engagement on cognition and grey matter volume cannot be explained by younger individuals' better performance and preserved grey matter.

4.1. Cognitive engagement and age of onset

Our results show that higher levels of cognitive engagement are associated with a delayed onset of the first symptoms in Huntington's disease patients and that lower levels of cognitive engagement are associated with an earlier onset. This is in line with a previous study on a murine model of Huntington's disease (van Dellen et al., 2000) which showed that those mice that were exposed to a stimulating environment presented a delayed onset of motor symptoms. Similar results have been observed in humans, where a passive lifestyle has been associated with an earlier onset in Huntington's disease (Trembath et al., 2010). However, the authors did not find higher levels of intellectual or physical activity to be related to a later onset of the symptoms. In a study on the impact of education – a component of CRQ – on Huntington's disease patients, López-Sendón et al. (2011) found that higher education was associated with less severe clinical symptoms in motor, cognitive and behavioral domains and an earlier age of onset. The authors interpreted this result as reflecting higher awareness of the first symptoms by the more highly educated patients. It is important to bear in mind that in the study by López-Sendón et al., the age of onset was estimated by the report of patients and their caregivers, while in the current study we took into account the difference between the actual age of onset and the theoretically predicted age of onset of motor symptoms.

4.1.1. Cognitive engagement and cognitive performance

After controlling for disease burden, CRQ scores were significantly associated with measures of working memory, inhibitory control and cognitive flexibility. Therefore, at the same stage of the disease according to the disease burden, those patients with higher CRQ scores showed better executive functions. Our results are consistent with previous studies on Huntington's disease showing the benefits of cognitive engagement in cognition (Bonner-Jackson et al., 2013; López-Sendón et al., 2011).

4.1.2. Neural effects of cognitive engagement in Huntington's disease

The present study investigates the modulation of EC-RSN and gray matter volume by the levels of cognitive engagement in Huntington's disease with the aim of studying the effects of a cognitively active lifestyle in the brain, both functionally and structurally.

Our results on the functional connectivity of the EC-RSN suggest a functional modulation of the ACC and the left AngG by cognitive engagement. In particular, we observed that higher CRQ scores were associated with a decrease in the strength of functional connectivity in the ACC, a region in which a reduced strength in functional connectivity has been linked to executive deficits in mild cognitive impairment (Wu et al., 2014b). We also observed a decrease in the strength of the negative functional connectivity patterns between the left AngG and the EC-RSN related to higher CRQ scores. The negative connectivity pattern observed between the EC-RSN and the AngG mirrors the typical anti-correlation coupling of the EC-RSN and the DMN (Fox et al., 2006, 2005). This could suggest that this region is acting as a potential cortical node, linking the EC-RSN to the DMN, given the fact that the left AngG, besides forming part of the EC-RSN, is also a core hub of the DMN. This interpretation is also in line with previous studies showing that the interaction between the DMN and the EC-RSN is altered in other neurodegenerative diseases (Rocca et al., 2012; Zhu et al., 2016). Furthermore, the DMN has been suggested to be the origin of the compensatory mechanism mediated by higher levels of cognitive engagement (Bozzali et al., 2015). In this regard, the role of parietal areas in compensatory process has previously been reported in Huntington's disease (Klöppel et al., 2015, 2009; Scheller et al., 2013).

After correcting for the level of cognitive engagement, we did not find significant relationship between performance in executive

functions and functional connectivity in either ACC or AngG. This lack of correlation could be interpreted in different ways. One possibility would be that at the same level of performance, a higher level of disruption in functional connectivity is needed in patients with higher levels of cognitive engagement. This would be a form of brain resilience, since a higher cognitive engagement would not protect from a reduction in functional connectivity but against its negative effects on cognitive performance. Alternatively, the observed pattern of reduced connectivity could represent an increase in network efficiency. According to this second interpretation, those individuals with higher CRQ scores would need less strength of connectivity to achieve similar performance on the cognitive tasks. In this case, a cognitively active lifestyle would confer brain resistance in the form of protection against a loss of neural efficiency. However, the current study does not allow to distinguish between these two different scenarios. In order to fully characterize compensatory mechanisms, longitudinal measures of brain activity should be combined with measures of changes in both the severity of brain pathology and performance (Gregory et al., 2017). Recently, increased effective connectivity between left and right DLPFC has been associated with more preserved cognitive function in Huntington's disease, showing a longitudinal pattern that suggests a possible compensatory mechanism (Gregory et al., 2018).

Regarding grey matter volume, our findings suggest that higher levels of cognitive engagement are associated with higher levels of brain resistance. Specifically, higher CRQ scores were associated with a reduced atrophy in the bilateral caudate, a particularly vulnerable region in Huntington's disease which is involved in executive functions. This is in line with those results reported by Bonner-Jackson et al. (2013). Moreover, we also observed an increase in gray matter volume associated with higher levels of cognitive engagement in the precuneus, which is also a core-hub of the DMN.

Our results are in line with converging evidence in neuroimaging studies that has shown the impact of life experience in brain plasticity, producing changes in gray matter volume (Draganski et al., 2004; Maguire et al., 2006) and studies on aging and Alzheimer's disease showing that a more cognitively active lifestyle is associated with lower levels of beta-amyloid pathology (Marks et al., 2012; Schreiber et al., 2016; Wirth et al., 2014), larger hippocampal volume (Schreiber et al., 2016) and greater brain weight (Brayne et al., 2010). In Huntington's disease, higher cognitive engagement has been found to be associated with slower rates of volume loss in caudate and putamen (Bonner-Jackson et al., 2013), which is consistent with our results. Studies in rodents have also associated stimulating environments with neurogenesis (van Praag et al., 1999) and upregulation of brain-derived neurotrophic factor (BDNF), which fosters neural plasticity and could provide brain reserve (van Praag et al., 2000). The importance of sensorimotor and cognitive stimulation in protecting against pathology and delaying the appearance of symptoms has also been reported in Huntington's disease mouse models (Benn et al., 2010; Lazic et al., 2006; Mazarakis et al., 2014). It has been proposed that cognitive engagement can increase both brain resistance and resilience and that the basis underlying them could be different. For instance, in Alzheimer's disease, brain resistance could be associated with higher clearance of beta-amyloid deposits (Arenaza-Urquijo and Vemuri, 2018; Xie et al., 2013), while brain resilience could be associated with the preservation of dendritic spines and neurite morphology (Boros et al., 2017; Perez-Nievas et al., 2013).

Finally, the current study presents some limitations that should be acknowledged. Firstly, age of onset was retrospectively reported by the closest relative of the patient. This measure of age of onset strictly depends on the level of awareness of the disease symptoms by the family members of the patient. Two other equally subjective possible measures of age of onset are the reports made by the patients themselves and those made by the clinician of reference. However, Huntington's disease patients are often unaware of their symptoms or they underestimate them. Therefore, Huntington's disease patients reports regarding age of onset may not be reliable (Sitek et al., 2014). Regarding the clinicians' reports, many patients do not visit a neurologist until they have unequivocal symptoms, hence the difficulty of obtaining a medical report that indicates an accurate the age of onset. Secondly, whilst in the actual age of onset any type of symptom was considered, the models currently available for the calculation of the theoretical age of onset only consider motor symptoms, since clinical diagnosis is made on the basis of this type of symptoms. Therefore, it is possible that part of the difference between actual and theoretical age of onset can be explained by the discrepancy in the type of symptomatic onset. Lastly, although the cross-sectional nature of our study does not allow us to address causal relationships it still provides useful information regarding the associations between lifestyle factors and disease progression.

In conclusion, our findings provide evidence of the association between a cognitively active lifestyle and both a delayed appearance of the first clinical symptoms and less severe cognitive deficits in Huntington's disease patients. This cognitive engagement may confer protection against brain atrophy and modulate the strength of connectivity of the EC-RSN related to executive function capacities. Longitudinal studies are nevertheless necessary to confirm this possibility. In view of these findings, we propose that interventions aimed at increasing engagement in cognitively stimulating activities in order to delay the appearance of the first symptoms and slowing its progression once the disease is manifest could be beneficial for Huntington's disease individuals. Future studies are needed to further investigate the effects of the different components of cognitive engagement and the brain changes that occur in the attempt to better cope with Huntington's disease pathology.

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Competing interests

The authors declare no competing interests.

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