



## The impact of bilingualism on brain structure and function in Huntington's disease



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### ABSTRACT

**Introduction:** Bilingualism exerts neuroprotective effects against neurodegeneration. In Huntington's disease (HD), the systems involved in bilingual control show early compromise, but the effect of bilingualism on the course of HD is unknown.

**Methods:** We addressed the impact of lifelong use of bilingualism on the clinical features, brain structure and function in 30 early-mild stage HD patients. Using voxel-wise regression analysis, we explored the effect of levels of use of bilingualism on grey-matter volume (GMV) and 18F-FDG metabolism.

**Results:** Higher use of bilingualism was associated with better performance in inhibitory control and set-shifting independently of age and education and with higher GMV in the inferior frontal gyrus. 18F-FDG data revealed a significant effect on multiple fronto-temporal regions, specifically, in the dorsal anterior cingulate cortex, the anterior insula, the ventromedial orbital prefrontal cortex and the inferior frontal gyrus. These changes contributed to better inhibitory control and set-shifting and to more preserved motor and functional capacity.

**Conclusion:** In HD, lifelong use of bilingualism is associated with structural and metabolic brain changes that have an impact on cognition, movement and functionality. These findings highlight the importance of stimulating cognitive and brain reserve in HD and in other neurodegenerative conditions.

### 1. Introduction

The learning and use of two or more languages during lifespan has been associated with neuroprotective effects against age-related cognitive decline, outcome after stroke, and delayed onset of dementia [1,2]. To select and speak one language without interference from the other, bilinguals display lifelong use of action monitoring and executive control mechanisms [3]. A well-known consequence of this continual use of two languages is that bilinguals exhibit better performance in linguistic and non-linguistic tasks requiring conflict monitoring, set shifting and inhibitory control [4]. This effect is explained by the

multimodality (non-language specificity) of the structures recruited to monitor and control two or more languages. Consequently, bilingualism tunes brain structures and networks that are critical for executive control, such as the dorsal-lateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC), the caudate nucleus, the temporal lobe, and the inferior parietal lobe [3]. Bilingualism is also associated with higher preservation of multiple white matter tracts and is known to influence resting-state functional brain activity as seen in the form of more efficient connectivity of the frontal-executive and the default-mode network [5,6]. Overall, lifelong use of bilingualism appears to enrich brain and cognitive reserve, leading to neuroprotective effects [2,6].

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Brain and cognitive reserve capacities moderate between brain pathology and clinical outcome. Brain reserve refers to the passive capacity of the brain (i.e.: more neurons or synapse) to deal with pathology whereas cognitive reserve refers to how the brain actively copes with brain pathology by using cognitive processes or by enlisting compensatory mechanism [24]. Although cognitive reserve has shown to positively impact cognitive performance and disease onset in Huntington's disease (HD) [12], almost nothing is known about the influence of bilingualism in this disease.

HD is a fatal neurodegenerative disorder that is fully explained by a single mutation of the *HTT* gene in the short arm of chromosome 4 [7]. HD usually manifests around mid-adulthood in all individuals carrying a CAG expansion of more than 38 repeats. Clinically, HD is characterized by progressive motor, cognitive and neuropsychiatric alterations that lead to complete loss of functional independence [7]. The primary neuropathological hallmark of HD is the massive loss of the medium spiny neurons of the basal ganglia, leading to marked atrophy of the caudate nucleus and putamen [8]. Functional alterations and degeneration of the prefrontal cortex (PFC), the ACC, the temporal lobes, and posterior-cortical territories also define HD [9]. Accordingly, deficits in set-shifting, inhibitory control, planning, verbal fluency, psychomotor speed and retrieval strongly define the cognitive phenotype exhibited by HD patients [10,11]. Most of these brain structures and cognitive functions that are affected in early HD have a critical role in the optimal control of bilingualism. However, the impact of bilingualism on HD has not been previously addressed.

Here we explore the effect of bilingualism in HD in a sample of early-stage bilingual HD patients. We addressed the degree of use and competence of bilingualism across the lifespan. We then assessed the impact of bilingualism on clinical parameters and on brain structure and metabolism by combining measures of grey-matter volume (GMV) and 18F-fluorodeoxyglucose (18F-FDG) metabolic uptake (SUVr).

## 2. Materials and methods

### 2.1. Participants

Thirty Catalan-Spanish bilinguals confirmed as gene mutation carriers (CAG  $\geq$  39) were prospectively recruited from the outpatient clinic of the Movement Disorders Unit at Hospital de la Santa Creu i Sant Pau. Informed consent was obtained from all individual participants included in the study. Participants were classified as early or mild-stage HD (Shoulson and Fahn stages 1 and 2) based on a total motor score on the Unified Huntington's Disease Rating Scale (UHDRS-TMS) greater than four and a total functional capacity (TFC) greater than seven [15,16]. We calculated the disease burden score (DBS), a measure of total exposure to mutant huntingtin across the lifespan, using the formula based on age and CAG length [ $\text{age} \times (\text{CAG} - 35.5)$ ] [17]. All participants were free of any neurological disorder other than HD. We excluded individuals with a history of traumatic brain injury, epilepsy, drug abuse, or non-compensated systemic disease (i.e.: diabetes).

Socio-demographic and clinical data included age, sex, education, age at diagnosis, cognitive status, presence and severity of neuropsychiatric symptoms, and use of medication. The use, exposure and competence of bilingualism across the lifespan were addressed using a modified version of the Anderson et al. bilingualism questionnaire [18]. A bilingualism index (BI) was defined and values were measured for BI relative to use (BIuse) and relative to competence (BIcomp). These values were computed according to the formula [ $BI = 1 - (\%L1 - \%L2)$ ], where % was based on the answers provided for the number items. BIuse provided a measure of how a person used both languages throughout life. BIuse = 1 indicates that a person used both languages equally (i.e.: speaking half the time in Spanish and half the time in Catalan), whereas a BIuse = 0.25 indicates that a person used one language 75% of time). Accordingly, the higher the BIuse, the higher the number of between-language switching throughout life. In contrast,

BIcomp measured proficiency writing, speaking and understanding the two languages. A BIcomp = 1 indicates that a person is highly proficient in both languages.

The study protocol defining all the procedures performed in the present study was reviewed and approved by the local research ethics committees at Hospital de la Santa Creu i Sant Pau in Barcelona. All procedures were performed in accordance with the Helsinki Declaration (1964) and its later amendments.

### 2.2. Behavioral and cognitive assessment

Behavioral assessment was addressed using the Problem Behaviors Assessment Scale for HD (PBA-s) [19]. This 11-item semi-structured instrument specifically focuses multiple neuropsychiatric symptoms related to HD, rating them according to frequency and severity.

Cognition was assessed through the cognitive subtests of the UHDRS (cogscore) and additional measures [16]. Assessment included the FAS test for phonetic verbal fluency, the semantic verbal fluency test, the symbol digit modality test (SDMT), the Stroop test, and the Trail Making Test parts A and B. In the FAS test and in the semantic verbal fluency test, we recorded the total number of words per letter and the total number of names of animals produced in one minute. In the SDMT, the total score was the total number of correct substitutions given in 90 s. In the Stroop test, the total score was the total number of correct responses in 45 s. In the TMT, the total score was expressed as the total time required to complete the task, with the maximum time being defined as 240 s. This assessment provided measures of frontal-executive performance, processing speed and attention.

### 2.3. Neuroimaging acquisition

T1-weighted MRI scans were acquired in a 3T Philips Achieva. MRI was performed using a specific axial T13D-MPRAGE MRI (TR/TE 500/50 ms, flip angle = 8°, field of view (FOV) 23 cm, with in-plane resolution of 256  $\times$  256 and 1 mm slice thickness). 18F-FDG PET/CT data were acquired on a Philips Gemini TF PET/CT 60 min after the intravenous injection of 277 MBq/ml of 18F-FDG. During the uptake phase, all participants were resting with eyes closed and ears plugged to reduce background stimulations. The reconstruction method was iterative (LOR RAMLA, three iterations and 33 subsets) with a 128  $\times$  128 matrix size included in a FOV of 256 mm, resulting in 2 mm pixel size and 2 mm pixel slice thickness. Time of acquisition was 10 min 18F-FDG PET/CT scans were performed according to the EANM procedure guidelines for PET brain imaging [20].

### 2.4. Data analysis

#### 2.4.1. Socio-demographic and clinical data

The participants' socio-demographic and clinical variables are expressed as means  $\pm$  standard deviations (SD) for continuous variables and as percentages for categorical variables. Multivariate logistic regression analysis was used to explore associations between the obtained imaging measures and clinical data.

#### 2.4.2. T1-MRI image analysis

Grey-matter volume (GMV) analysis from T1-weighted images was performed by a voxel-based morphometry (VBM) analysis using the Statistical Parametrical Mapping (SPM12) software package [<http://www.fil.ion.ucl.ac.uk/spm/>]. Segmented GMV maps for each subject were normalized to the Montreal Neurological Institute (MNI) space by applying DARTEL transformations. The resulting GMV maps were smoothed using an isotropic spatial filter of 8 mm full-width at half maximum (FWHM) to reduce inter-individual variability.

These normalized and smoothed GMV images were entered into a voxelwise regression analysis to study the effect of the different IB scores. Age, sex, education, total intracranial volume (TIV), CAG length,

and UHDRS-TMS were used as covariates within the model.

Finally, GMV values for each patient were computed at the identified clusters using build-in SPM functions to perform further regression analyses with other clinical variables of interest.

### 2.4.3. 18F-FDG PET image analysis

Brain glucose metabolism analysis, as measured by 18-FDG PET relative standardized uptake value (SUV<sub>r</sub>), was performed using SPM and the biological parametric mapping (BPM) toolbox [21]. First, 18F-FDG PET scans were intensity scaled by the mean tracer uptake within the pons-cerebellar vermis reference region [22] to obtain SUV<sub>r</sub> images. These images were then spatially normalized to the MNI space, and smoothed using a Gaussian kernel of 12 mm FWHM.

Next, the resulting images were entered into a voxelwise regression analysis to study the effect of IB scores into brain metabolism. The following covariates were used: Age, sex, education, CAG length, and UHDRS-TMS. Additionally, partial volume correction to control for the effect of a possible underlying atrophy within the voxelwise model was performed by entering each subject's GMV map in MNI space as a voxelwise covariate within the model.

SUV<sub>r</sub> values at the identified clusters were computed for each patient using build-in SPM functions to perform further regression analyses with other clinical variables of interest.

In both imaging modalities, clusters surviving  $p < 0.05$  corrected for family-wise error (FWE) were considered significant. For exploratory and depicting purposes, we also report results showing  $p < 0.001$  (uncorrected) and a minimum extent of  $k = 100$  voxels.

## 3. Results

### 3.1. Clinic and sociodemographic data

Thirty participants (CAG =  $44 \pm 3$ ; age =  $52 \pm 10$ ) completed all the study procedures. Participants' characteristics are summarized in Table 1. As seen, the mean UHDRS-TMS score was  $32 \pm 17$  and the TFC was  $10.3 \pm 2$ , confirming all participants were stage 1 or 2 and thus classified as early and mild HD.

**Table 1**  
Clinical and sociodemographic characteristics.

	Participants
Age (years)	$52.5 \pm 11$
Gender (f/m)	20/10
Education (years)	$11.7 \pm 5$
CAG length	$43.7 \pm 3$
DBS	$407 \pm 90$
UHDRS-TMS <sup>a</sup>	$33 \pm 17$
TFC <sup>b</sup>	$10 \pm 2.5$
PBA-s total score <sup>c</sup>	$8.6 \pm 5$
COGSCORE <sup>d</sup>	$152 \pm 76$
FAS <sup>e</sup>	$17.6 \pm 12$
SDMT <sup>f</sup>	$22 \pm 13$
Stroop	
Color	$37.1 \pm 19$
Word	$54.3 \pm 26$
Word-color	$19.2 \pm 13$
Interference score	$-2.6 \pm 6.8$
TMT-A (seconds)	$96.5 \pm 60$
TMA-B (seconds)	$201.4 \pm 69$
TMT-B – TMT-A <sup>g</sup>	$1.6 \pm 1.2$
Semantic verbal fluency (animals)	$11.3 \pm 4.2$

<sup>a</sup> Unified Huntington's Disease Rating Scale – Total Motor Score.

<sup>b</sup> Total Functional Capacity.

<sup>c</sup> PBA apathy score.

<sup>d</sup> UHDRS cognitive score.

<sup>e</sup> Phonetic verbal fluency using letters F, A and S.

<sup>f</sup> Symbol Digit Modality Test.

<sup>g</sup> Subtraction TMT-B minus TMT-A.

The mean BIuse relative to use and exposure of two languages across the lifespan was  $0.4 \pm 0.2$  and followed a homoscedastic distribution between 0.08 and 1. The BIcomp was  $0.6 \pm 0.3$ . Whereas competence appeared significantly associated with educational level ( $r = 0.653$ ;  $p < 0.001$ ), no significant correlations were found between BIuse, age and education.

Focusing on BIuse, higher scores appeared significantly associated with better performance on the Stroop word-color interference ( $r = 0.389$ ;  $p < 0.05$ ) and completion time on the TMT-B ( $r = -0.403$ ;  $p < 0.05$ ), independently of the educational level and age. Thus, when controlling for the effect of age and education, IBcomp was not associated with any measure.

### 3.2. MRI results

In the MRI analysis no clusters survived correction for multiple comparisons ( $p < 0.05$  FWE). A single uncorrected cluster was found in form of higher GMV in the right inferior frontal gyrus associated with higher BIuse (Fig. 1; Table 2). GMV measured for each participant in the identified cluster showed a positive association between GMV in right inferior gyrus and better performance on the Stroop word-color interference ( $r = 0.492$ ;  $p < 0.01$ ) and TMT-B time of completion ( $r = -0.419$ ;  $p < 0.05$ ).

### 3.3. 18F-FDG PET/CT results

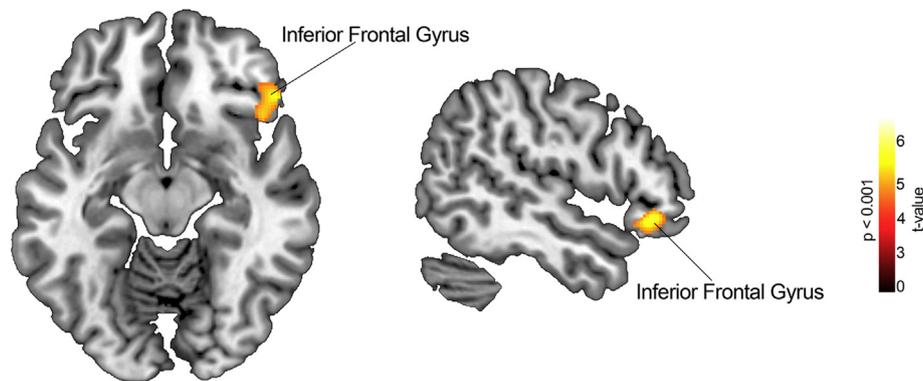
In the 18F-FDG analysis (Fig. 2; Table 2), higher BIuse was strongly associated with increased SUV<sub>r</sub> in a set of fronto-temporal regions, independently of GMV atrophy. Specifically, higher BIuse was associated with a bilateral higher glucose metabolism in the dorsal ACC (dACC), the ventromedial orbital PFC (vm-OPFC), the insula, the superior OPFC, the left orbital BA 47, the left inferior frontal gyrus and the right inferior temporal gurus (Fig. 2; Table 2).

After calculating the SUV<sub>r</sub> uptake in all the identified clusters, we found a set of significant associations between the modulation exerted by the BIuse and clinical measures. Increased SUV<sub>r</sub> in the dACC was strongly associated with better performance on the Stroop word-color interference ( $r = 0.514$ ;  $p < 0.01$ ). Increased SUV<sub>r</sub> in the left BA47 was associated with a lower UHDRS-TMS score ( $r = -0.496$ ;  $p < 0.01$ ) and better functional capacity as assessed through the TFC ( $r = 0.546$ ;  $p < 0.01$ ). Increased SUV<sub>r</sub> in the left insula was associated with better Stroop interference performance ( $r = 0.497$ ;  $p < 0.01$ ). Significant associations were also found between higher irritability scores and lower SUV<sub>r</sub> in the inferior frontal gyrus ( $r = -0.389$ ;  $p < 0.05$ ), lower SUV<sub>r</sub> in the superior OPFC ( $r = -0.369$ ;  $p < 0.05$ ), and lower SUV<sub>r</sub> in the insula ( $r = -0.413$ ;  $p < 0.05$ ).

## 4. Discussion

Our results show that more frequent lifelong use of bilingualism is associated with significant changes on 18F-FDG metabolic uptake in a set of brain regions and a slight tendency of increased GMV in a single frontal region. This effect exerts a strong impact on cognitive measures related to inhibitory control and cognitive flexibility. These results suggest that, even in this devastating disease, higher use of bilingualism moderates the degree of neural integrity and clinical expression of neurodegenerative disorders.

Our findings concerning better executive control in bilinguals are congruous with previous reports both in healthy and clinical populations. In healthy controls, use of bilingualism tunes the functional and structural brain architecture in an experience-dependent manner and these changes have a significant impact on task performance [5]. Specifically, the dACC is critically sensitive to use of bilingualism [4,23]. Given the role exerted by the dACC on conflict monitoring, bilinguals exhibit better performance to solve cognitive conflict in domain-general cognitive tasks [4,5]. Similarly, the effects of bilingualism have been



**Fig. 1.** Results of the voxel-based morphometry analysis of the structural T1-weighted images. The slices show regions of a significant GMV increase in association with lifelong bilingualism use. For depiction purposes results are showed with a  $p < 0.001$  (uncorrected) and  $k = 100$ .

**Table 2**

Results of the voxel-based morphometry analysis of GMV and 18F-FDG.

Anatomical region	Cluster size	T value	MNI coordinates (x, y, z)
<b>Voxel-based morphometry analysis of GMV</b>			
Right inferior frontal gyrus	355	5.80	51, 32, -9
<b>Results of the 18F-FDG PET analysis</b>			
vmOPFC/Insula/sup OPFC/dACC <sup>a</sup>	2863	5.59	12, 38, -24
Right inferior temporal gyrus <sup>a</sup>	1301	5.53	52, -42, -26
Left mid inferior frontal gyrus/left BA47 <sup>a</sup>	1366	4.49	-38, 48, -8
Right sup frontal gyrus	334	4.98	20, 26, 58
Left ACC	264	4.11	-6, 38, 24
Right supramarginal gyrus	193	4.27	64, -46, 32
Left inferior temporal gyrus	176	4.49	-56, -32, -20
Right precentral gyrus	138	4.09	64, 4, 29
Left DLPFC	129	4.90	-38, 14, 34

<sup>a</sup> Clusters surviving  $p < 0.05$  FWE.

noted on structures mediating set-shifting and cognitive flexibility such as the DLPFC [5,23].

Regarding neurodegenerative diseases, multiple mechanisms participate in age-of-onset and in the clinical course of the disease [24]. Brain and cognitive reserve are currently recognized as modeling factors of aging and neurodegeneration [25]. Use of bilingualism has shown to be an important aspect of cognitive and brain reserve enrichment [26]. Thus, in mild cognitive impairment and Alzheimer's disease, it appears to delay the onset of dementia for up to 4.5 years. Use of bilingualism also appears to mitigate the functional disintegration of networks such as the default mode network and the central executive network, which is associated with a better global cognitive performance [1]. Preservation of white matter integrity has also been associated with use of bilingualism and a more benign course of cognitive deterioration in the context of aging [5,6].

Here we demonstrate that in HD, in absence of an association with age, education, and DBS, higher use of bilingualism contributes to better performance in tasks requiring inhibition, attention, anticipation, monitoring, and task-switching [27] and that these effects were independent of the level of competence in each language. Consistent with previous reports, higher use of bilingualism in our sample was also associated with higher GMV in the inferior frontal gyrus, possibly reflecting greater structural integrity.

Whereas these GMV changes appeared to be circumscribed to small territories, they exerted a significant impact on cognitive performance. Specifically, they notably modulated inhibitory control as observed in the better performance in the Stroop interference condition.

In the 18F-FDG analysis, higher use of bilingualism was associated with a widespread pattern of increased metabolism in multiple fronto-

temporal regions. Specifically, the most robust effects were seen on the dACC, the ventro-medial orbital PFC, the anterior insula, the inferior temporal gyrus, and the DLPFC. Importantly, quantifications of SUVr in all these regions showed that higher 18F-FDG metabolism led to better performance in inhibitory control and set-shifting and better motor and functional status. This shows that the effects that use of bilingualism exerted on brain function had a positive impact on motor and functional outcomes.

Progressive loss of GMV and 18F-FDG uptake is evident in the course of HD [14,28]. These changes can be tracked as early as 15 years before the first clinical manifestations of the disease and are strongly associated with the motor, cognitive and behavioral signs and symptoms defining the clinical picture of HD. All these structural and functional changes occur during HD progression and contribute to the complex presentation of this disease [29]. Among these changes, disruption of the neural circuitry underlying inhibitory control and action monitoring is evident in both premanifest and early HD in the form of progressive damage to many brain regions such as the SMA, the ACC, the insula, and the medial frontal cortex [9,14]. Changes in these regions are strongly associated with deficits in response inhibition and action monitoring [30] and could contribute to characteristic behavioral disturbances such as poor temper control, irritability and dys-executive behavior. From a neuropsychological testing perspective, damage of this circuitry can be inferred based on difficulties in tasks such as in Go/NoGo paradigms or in the Stroop interference condition. Accordingly, our data show an expected association between structural and functional changes in nodes of the action monitoring system and in performance on the Stroop interference. However, we show that the degree of damage along this circuitry and its impact on cognitive performance is positively modulated as a function of greater lifelong use of bilingualism.

Our data, however, do not provide evidence supporting an effect of bilingualism on key pathological hallmarks of HD such as the caudate nucleus and the putamen. This may be because basal ganglia atrophy is already prominent in symptomatic participants with early and mild stages of the disease.

The absence of a matched sample of monolingual HD participants may be a limitation. By including such a group in a cross-sectional study of this type we could have compared the clinical status of two groups of the same age at disease onset and with similar CAG length. A second limitation is the absence of follow-up data as this would have allowed us to study possible differences in disease progression as a function of use of bilingualism. This could be of particular interest to explore whether the observed changes are already present in premanifest individuals and whether they have an impact on age of onset and disease progression.

In conclusion, the present study shows that lifelong use of bilingualism has a positive effect on structural and functional brain integrity in

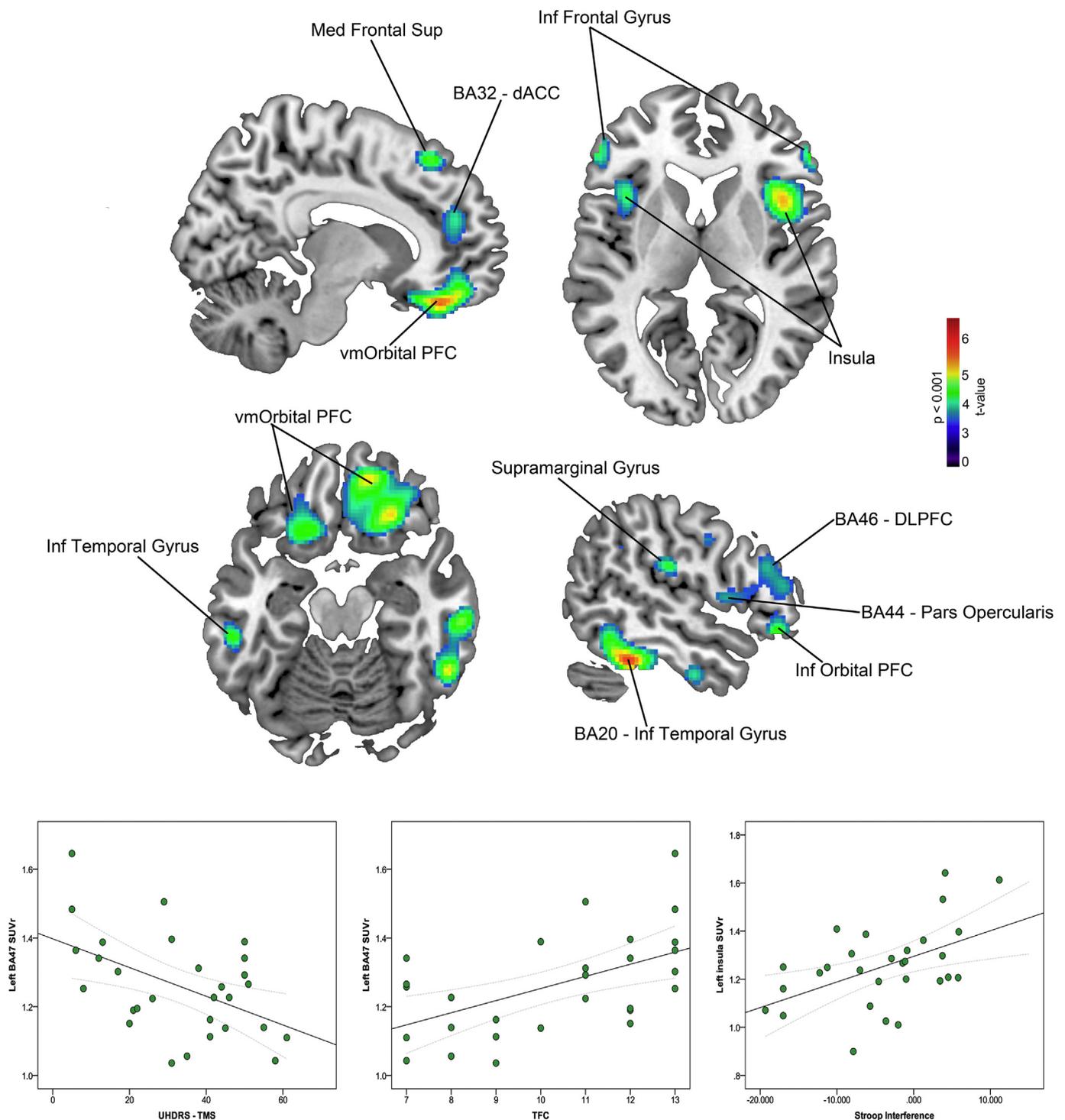


Fig. 2. Top: Results of the voxelwise analysis of the 18F-FDG PET scans. The slices show regions of significant SUVR increase in association with lifelong bilingualism use. For depiction purposes results are showed with a  $p < 0.001$  (uncorrected) and  $k = 50$ . Bottom: Correlations between SUVR and other clinical measures.

early and mild HD. Essentially, this effect benefits on cognitive, functional and motor status that is not explained by years of education or level of linguistic competence. These data highlight the positive effect of cognitive and brain reserve enrichment as modulators of the neuropathological process associated with neurodegenerative conditions.

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